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PANEL DISCUSSION ON THE CLINICAL MANAGEMENT OF HYPERTENSION*

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MODERATOR MASTER: I have before me many questions which I have attempted to organize to cover the topics related to hypertension in which I think you will be interested.

I shall start with Doctor Perera. *Which is the preferable expression, "hypotensive" or "antihypertensive" drug therapy?*

DR. PERERA: "Antihypertensive" would be the more nearly correct term. We are combating hypertension rather than trying to decrease the blood pressure to a low level.

MODERATOR MASTER: *Would you treat a patient for hypertension, if he had no sign or symptom attributable to it?*

DR. PERERA: I would treat the patient. I might not treat the disease.

MODERATOR MASTER: If he had no sign or symptom, you would pay no attention to the hypertension?

DR. PERERA: That is right.

MODERATOR MASTER: When would you give a drug? *For what clinical reasons would you prescribe antihypertensive drugs?*

DR. PERERA: I would give drugs for symptomatic purposes when a patient needed them. I would reserve the stronger drugs, such as ganglionic blocking agents, for those forms of hypertension in which there was evidence of real acceleration, particularly evidence of arteriolar damage.

MODERATOR MASTER: If a patient had retinopathy, would you then dispense an antihypertensive drug?

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DR. PERERA: Yes. I would consider it, among other forms of treatment.

MODERATOR MASTER: If the patient had an enlarged heart?

DR. PERERA: No. That would not be an indication.

MODERATOR MASTER: If the patient had hypertension and an enlarged heart?

DR. PERERA: That would not be a good indication.

MODERATOR MASTER: If a patient had hypertension and congestive failure, would you prescribe an antihypertensive drug?

DR. PERERA: I would not give it until I had exhausted other measures to combat congestive failure. At times, a ganglionic blocking agent may be an adjunct to the treatment of congestive failure.

MODERATOR MASTER: If a patient had hypertension and had had a cerebrovascular accident, would you prescribe an antihypertensive drug?

DR. PERERA: I would prescribe nothing other than a sedative or a mild tranquilizing drug, because I would be afraid of too great a fall in blood pressure and the possible consequences.

MODERATOR MASTER: Dr. Moser, *what is your routine procedure once you have decided to administer antihypertensive drugs to a patient?* Do you start with sedatives?

DR. MOSER: I do, unless the patient is critically ill, in which case rapid lowering of blood pressure might be indicated. Generally, we start with the milder agents.

MODERATOR MASTER: Which do you consider the mildest, and which has the fewest side-effects?

DR. MOSER: The rauwolfia preparations are the mildest agents and, as such, they do not have potent blood pressure-lowering ability. In our experience, it makes no difference whether the whole root or a purified derivative is used.

MODERATOR MASTER: I mean rauwolfia in comparison with ganglionic blocking agents. Which do you think is the more potent group?

DR. MOSER: Among drugs with mild action, the rauwolfia preparations are as satisfactory as any of the tranquilizers or sedatives that we have been using. They are so mild that we would start with these drugs in the patient who requires active therapy. We would be inclined to add hydralazine or one of the ganglionic blocking agents fairly early in the course of treatment if there is any organ system involvement and a persistently high diastolic blood pressure.

MODERATOR MASTER: When would you proceed with the ganglionic blocking agent? I wanted you to tell us whether or not the ganglionic blocking agents are more potent than the other drugs.

DR. MOSER: They are much more potent.

MODERATOR MASTER: For the moment, I should like to ask some general questions. Later we shall discuss the drugs that Dr. Perera and Dr. Moser have mentioned.

Dr. Moser, *do you recommend that the patient learn to take his own blood pressure at home?*

DR. MOSER: No. We have not been doing that except on rare occasions. The patient is conscious enough of blood pressure without adding the extra burden of having him measure it at home, or having a member of his family do so.

MODERATOR MASTER: Dr. Perera, do you disagree?

DR. PERERA: For the most part, I agree. There are a few intelligent, cooperative people who can take their own blood pressures but, as Dr. Moser implied, the selection depends upon the patient rather than upon the routine.

MODERATOR MASTER: Dr. Smithwick, have you any different thought? Do you think the patient should ever take his own blood pressure?

DR. SMITHWICK: I agree with Dr. Perera. Some patients are so constituted that it is probably better for them to do it. They actually do determine their pressures and don't seem to be upset over it. However, as a general rule, I would not be in favor of it.

MODERATOR MASTER: Dr. Fishberg?

DR. FISHBERG: I have never had a patient take his own blood pressure, so I cannot give an opinion based on convincing evidence. From what I have heard from others who do so, and from what I have read, I am by no means convinced that it is possible in that way to obtain results superior to those obtained by one's own careful observation, even though the blood pressure is taken less often.

MODERATOR MASTER: Dr. Fishberg, if a patient with very high blood pressure—260 systolic and 140 diastolic—has retinopathy and is receiving mecamylamine (Inversine), do you not want to see him at least once a week?

DR. FISHBERG: The treatment of all such patients should be started in the hospital. I do not care to start ganglionic blocking agents outside the safety of the hospital.

MODERATOR MASTER: Dr. Smithwick, *at what blood pressure level would you start treatment?* I mentioned 260/140 mm. If you had such a patient, would you have your internist proceed with drug therapy first?

DR. SMITHWICK: Something should be done to lower a blood pressure elevated to that height, even if the patient has no symptoms of any consequence. I strongly believe, on the basis of experience, that there is a relationship between the severity of the hypertension and the prognosis.

MODERATOR MASTER: *What type of patient do you think unsuited for antihypertensive drug therapy?*

DR. SMITHWICK: My idea is that, if the drug therapy is to be really effective, perhaps one of our great opportunities is to treat people in the early stages of the disease, and try to prevent the development of cardiovascular changes. Our aim is normal life expectancy.

MODERATOR MASTER: Would you always give medical treatment first?

DR. SMITHWICK: The earlier in the disease, the more desirable it is to treat the patient medically. The more advanced the disease, the less desirable.

MODERATOR MASTER: Dr. Fishberg, apropos of the question I asked Dr. Smithwick—would you treat a man 85 years of age with antihypertensive drugs, if he has hypertension and advanced atherosclerosis? If he has chronic uremia? In other words, *are there any contraindications to antihypertensive drug therapy?*

DR. FISHBERG: There certainly are. Some people have lost their lives because antihypertensive drugs were given when they were contraindicated. Most of the symptoms that accompany hypertension are due to the atherosclerosis that

develops in all hypertensive persons as the years pass. There are symptoms due to the hypertension. The so-called malignant picture is a manifestation of very high diastolic pressure modified by some other factors. This condition accounts for only a small proportion of cases of hypertension. It used to be 7 per cent in New York City, but it is considerably less now.

Most of the patients have symptoms due to coronary or cerebral atherosclerosis. If these symptoms dominate the clinical picture, care must be exercised in the use of antihypertensive drugs, because, when the blood pressure is lowered, the blood flow through the heart or brain may become deficient.

In the early days of the use of potent hypotensive drugs I observed some fatalities due to deficient cerebral blood flow, and others due to deficient coronary blood flow. One cannot be too careful. It is necessary to analyze the picture. How much is due to high blood pressure? How much is due to concomitant atherosclerosis of large vessels?

I should add that, in advanced renal disease, a powerful hypotensive drug may precipitate uremia.

MODERATOR MASTER: Dr. Fishberg, if you had a man 75 years old with profound hypertension (I know this is not very common in the aged) and advanced arteriosclerosis, what would you do—refer him to Dr. Smithwick?

DR. FISHBERG: I believe that hypertension at the age of 75 should not be treated with hypotensive drugs. I doubt that Dr. Smithwick would operate on a 75-year-old man. The use of a powerful hypotensive drug is not indicated at this age, and so I have never used one under these circumstances. In my experience with persons over age 60, none has been helped by hypotensive drugs, with the exception of those who experienced sedative, bradycardiac, and perhaps psychologic effects from rauwolfia.

MODERATOR MASTER: Dr. Fishberg, *have you any office procedure that would help us to determine whether or not a patient should receive an antihypertensive drug and whether it will do him any good?* Do you use Mendlowitz's test? What is your thought on that?

DR. FISHBERG: I doubt whether any of the so-called objective tests offer anything more than conventional clinical studies. Are you referring to plethysmographic measurements?

MODERATOR MASTER: That is right.

DR. FISHBERG: I have had no experience. I have seen only what other people have done with some of these cases. I doubt that they accomplish much.

MODERATOR MASTER: The theory is that whenever there is a neurogenic factor, antihypertensive drugs may be effective. Isn't that the principle?

DR. FISHBERG: I am not sure about describing certain cases as neurogenic in origin. I am not in a position to decide that a patient's hypertension is due primarily to overactivity of the sympathetic vasoconstrictor nerves.

MODERATOR MASTER: Dr. Perera, have you any ideas on that? I wish the panelists would interrupt whenever they so desire. I am moving rapidly solely to cover more ground, but if there is a difference of opinion, we want it; and if there is any suggestion, we want it.

Dr. Perera, do you think any office procedure can help to ascertain whether a patient will be benefited by antihypertensive drugs?

DR. PERERA: No.

MODERATOR MASTER: You agree too, no doubt, that clinical judgment is best. Would you try large doses of sedatives?

DR. PERERA: No. The response to rest or sedation may give an idea as to the lability of the hypertension but, in my opinion, it does not determine what the over-all response to treatment may be. The blood pressure will respond more readily to nerve section or blockade in patients with a labile blood pressure, but I do not think that is a true yardstick of prognosis.

MODERATOR MASTER: Dr. Perera, *what antihypertensive drugs can be employed parenterally?*

DR. PERERA: Many of the preparations are available in forms for parenteral administration. Rauwolfia can be given parenterally, and many of the ganglionic blocking agents. I never use them parenterally, even in so-called hypertensive crises, because I am not quite sure what these crises are. Many resolve themselves. Other represent cerebrovascular accidents, and there may be some danger in acute lowering of blood pressure at such times.

MODERATOR MASTER: Can the ganglionic blocking drugs be administered parenterally?

DR. PERERA: Yes.

MODERATOR MASTER: Can you do this with Inversine and some of the other preparations?

DR. PERERA: There are parenteral forms of veratrum derivatives as well as of many of the ganglionic blocking agents.

MODERATOR MASTER: Dr. Moser, you have gathered that Dr. Perera is conservative on the question of drugs. Do you employ antihypertensive drugs parenterally?

DR. MOSER: I agree with Dr. Perera that the occasions for using them are very limited. With the introduction of mecamylamine (Inversine), an orally effective, completely absorbed, ganglionic blocking agent, the need is reduced to the few patients unable to take anything by mouth. We have occasionally used parenteral therapy in such patients, provided they did not have uremia or marked oliguria. We find no parenteral use for veratrum derivatives, however, because the therapeutic dosage is so close to the toxic dosage that most people become ill from the use of these agents. We have used reserpine intramuscularly. Occasionally, in toxemia of pregnancy with nausea and vomiting and high blood pressure, we have used hydralazine (Apresoline) parenterally. In rare instances, we have used a slow intravenous infusion of pentolinium (Ansolysen) or Inversine.

I might disagree on one point. Although I agree with Dr. Fishberg and Dr. Perera that in many cases of hypertension with cerebral involvement (either following a cerebrovascular accident or encephalopathy) there is some danger in acute lowering of the blood pressure, we have seen several cases of cerebrovascular accident or encephalopathy with a high spinal fluid pressure in which

there has been dramatic benefit from this procedure. If the patient is so ill that nothing else can help, the drug may be used cautiously. In several instances we have been rewarded with a gratifying result.

MODERATOR MASTER: When you use the word "cautiously," you are "cautious." I agree. In cases of angina pectoris, however, I have seen acute coronary insufficiency precipitated because of the drop in blood pressure induced by antihypertensive drugs. I have not seen coronary occlusion. Therefore, I would say that, when angina pectoris is present and antihypertensive drugs are used, the systolic blood pressure should not be permitted to drop below 120–150 mm. Hg. Even with a blood pressure of 150 mm. in such a patient, upon standing the blood pressure may drop to 80 mm.

Dr. Moser, *would you allow a patient with severe hypertension to have salt, or would you prescribe a low-salt diet? Would you combine salt restriction and an antihypertensive drug?*

DR. MOSER: It has been shown that drastic restriction of sodium *will* enhance the effect of any drug therapy.

MODERATOR MASTER: Suppose the patient does not have heart failure?

DR. MOSER: I was about to say that, unless sodium restriction is carried to a completely impractical level (below 300 mg. a day or, at most, 500 mg.), blood pressure is rarely affected. Therefore, we do not restrict sodium unless congestive heart failure is present. Most of our patients are given fairly free diets (between 3 and 5 Gm. of sodium daily).

MODERATOR MASTER: You are being very temperate. If one prescribes antihypertensive drugs and restricts the salt intake considerably, is there not danger of postural hypotension?

DR. MOSER: There is danger of the patient stopping all treatment because of a double inconvenience—diet *and* drugs.[1]

MODERATOR MASTER: We agree. You would restrict the salt intake only when heart failure is present. Is that right?

DR. MOSER: Yes.

MODERATOR MASTER: Any disagreement? Dr. Fishberg.

DR. FISHBERG: I believe firmly, much more firmly than I did a few years ago, in the value of sodium restriction. For a long time I was skeptical about it, but in the last few years I have come to think it is of tremendous importance. Sodium must be restricted to less than 500 mg. a day before there is any chance of demonstrable lowering of the blood pressure within a relatively short period of time. I now also believe that lesser degrees of sodium restriction may slow the progress of hypertensive disease, and this is what brings me to that point of view.

[1] *Addendum* (January 1958): During the past year, we have been using a new orally effective, nonmercurial diuretic, chlorothiazide (Diuril) in most of our hypertensive patients. Patients may be allowed a fairly liberal sodium intake while receiving continuous diuretic therapy. Diuril (0.5 to 1 Gm. a day) has been most effective in combination with other drugs. In many instances we have been able to reduce the dosage of the more potent ganglionic blocking agents without loss of the blood pressure-lowering effect. Patients feel better when taking smaller dosages and the number of beneficial responses has increased since the introduction of this drug.

Among the patients in the hospitals where I work, and among the private patients that I see, so-called malignant hypertension is disappearing. We have few cases nowadays. Fifteen or twenty years ago, we sometimes had 4 or 5 cases of malignant hypertension at a time in the wards. We do not see nearly as many now, and have to look for some cause. I do not believe that a change has occurred in the biology of the disease in the past two decades. It is in hospitals where there are many so-called underprivileged patients—in New York City in hospitals where a large proportion of the patients are Negroes—that malignant hypertension is mostly found. The only way I can account for the difference is because of something that we have done in recent years. Today, practically every patient with elevated blood pressure is receiving a sodium-restricted diet.

MODERATOR MASTER: Dr. Fishberg, do you employ salt restriction in severely hypertensive patients? Do you use it when an antihypertensive drug is given?

DR. FISHBERG: Yes, every day.

MODERATOR MASTER: How strict would you be in salt restriction? Would you give a gram, half a gram, 300 mg., or 100 mg. of salt a day?

DR. FISHBERG: In severe hypertensive disease, I usually try to restrict the sodium intake to 500 mg. daily. Unfortunately, urinary measurements show that I do not always succeed.

MODERATOR MASTER: Would you prescribe 10 mg. of Inversine three times daily to a patient and continue a 200-mg. sodium diet for months? I am carrying this to the extreme to make a point.

DR. FISHBERG: I would continue a hypotensive drug with sodium restriction. Sodium is restricted in each of my patients who receives hypotensive drugs.

MODERATOR MASTER: Is that at a level of 200 mg. daily?

DR. FISHBERG: It is exceptional that anybody outside of a hospital will adhere to a 200-mg. sodium diet.

MODERATOR MASTER: Dr. Perera, do you agree? Would you use strict sodium limitation?

DR. PERERA: I am in the middle of the road. There are some definite indications for sodium restriction, but it is a rare patient, as Dr. Moser said, who can stick to it. I often prescribe a relatively low sodium intake. I don't know whether it does any good or not, but perhaps it is good training.

MODERATOR MASTER: Yes, but low sodium is the point I wish to make. I can see where you would cut it to 1 or 2 Gm. but, in my limited experience, it has been extraordinarily difficult and even hazardous to give a patient with severe hypertension (without heart failure) a 200-mg. sodium diet for any length of time.

DR. PERERA: I am not sure that it would be hazardous, but certainly difficult.

MODERATOR MASTER: Dr. Moser?

DR. MOSER: I agree. I think it would not be hazardous. Sometimes a good result is obtained, but it is almost impossible in an ambulatory patient.

MODERATOR MASTER: Good! We are having differences of opinion.

Many questions are waiting for you, Dr. Smithwick. *Has psychoanalysis ever helped hypertensive patients?*

DR. SMITHWICK: I have not seen a great deal of it tried. I know of no statistics on the subject.

MODERATOR MASTER: I have never sent a hypertensive patient to a psychoanalyst. Would you think one could help?

DR. SMITHWICK: They write books on it.

MODERATOR MASTER: Is there proof that the psychoanalyst can prevent hypertension and coronary occlusion?

DR. SMITHWICK: No matter who the physician treating a hypertensive patient may be, he can probably handle any psychiatric aspects of the problem as well as a psychiatrist. That is my belief. It is very important to remember that in many of these patients there is a definite pattern; they are high-strung people.

MODERATOR MASTER: You think the psyche plays an important role.

DR. SMITHWICK: It is important to try to have the patients change their philosophy a little in addition to whatever you do specifically for them.

MODERATOR MASTER: I think we all agree that the psyche is of tremendous importance. I did not know whether all would agree that psychoanalysts do not help except under the most unusual circumstances. Does anyone want to differ?

DR. FISHBERG: I see no reason for a patient with high blood pressure to be sent to a psychiatrist, as long as he has no manifestations that would lead one to send him to a psychiatrist if his blood pressure were not high.

MODERATOR MASTER: Dr. Fishberg, *what is your definition of accelerated or malignant hypertension?*

DR. FISHBERG: The accelerated form of hypertension is the title that Dr. Dana Atchley and Dr. Perera introduced for what previously had been called by others the malignant phase of hypertension. It covers those patients with high blood pressure in whom we have good reason to assume that many manifestations are due to the height of the diastolic pressure. I am afraid Dr. Perera will differ with me completely.

MODERATOR MASTER: Do you, Dr. Perera?

DR. PERERA: Starting with the definition, I agree that it represents a characteristic pathologic picture which one does not see during the patient's life. There is more and more reason, for looking on the accelerated form of hypertension as something specific and unique. It has a peak incidence at ages 38 and 39, and a sex distribution which is different from that of primary (essential) hypertension. There are a few instances of patients with so-called "malignant" hypertension without marked elevation of the blood pressure. I am not yet convinced that the level of the blood pressure is the determining factor in the accelerated form of the disease.

MODERATOR MASTER: Dr. Perera, *given a young man, aged 20 years, with a blood pressure of 150/90, would you prescribe an antihypertensive drug?*

DR. PERERA: No worries, no signs, no symptoms?

MODERATOR MASTER: He has this blood pressure continuously.

DR. PERERA: No. I would not.

MODERATOR MASTER: You would not.

Will you, please, say a word about rauwolfia compounds. How do they act?

DR. PERERA: Rauwolfia compounds presumably act upon the hypothalamus. They may act upon the temporal lobes of the brain as well. There are suggestions that they may be related in some way to 5-hydroxy-tryptamine (serotonin), which is present in some of the cells of the hypothalamus. From 30 to 40 per cent of patients receiving these preparations obtain tranquilizing effects and some lowering of the blood pressure.

MODERATOR MASTER: What preparations would you employ, if you wanted to use rauwolfia?

DR. PERERA: The preparation makes little difference. The pure alkaloid and the crude preparations appear to be about equal in their effects.

MODERATOR MASTER: What are some of the contraindications?

DR. PERERA: An increasing number of patients receiving ordinary dosages experience marked mental depression and sometimes even psychotic reactions. Rarely, a patient may become edematous, even to the point of congestive failure in the absence of heart disease. Nasal congestion may become excessive.

MODERATOR MASTER: Would you say it is contraindicated in congestive failure?

DR. PERERA: No. Usually, it has no effect on the state of congestive failure, but in an occasional patient there may be an increase in edema.

MODERATOR MASTER: I am glad you said that. My experience has been that, occasionally, a patient seems to become intractable to antidiuretic therapy.

Is rauwolfia expensive?

DR. PERERA: Not very.

MODERATOR MASTER: What is the range of expense in drug therapy? I think that Dr. Smithwick ought to comment here, because I have come across one or two articles in life insurance journals which stated that sympathectomy may be much cheaper than drug therapy. Did you know that?

DR. SMITHWICK: You have read that?

MODERATOR MASTER: Yes, I have.

DR. SMITHWICK: I can only say that I know of no comparative figures on cost of treatment.

DR. PERERA: I agree with that. It is much cheaper to send a patient to Dr. Smithwick than to continue large doses of some of the ganglionic blocking agents for several years.

MODERATOR MASTER: In the December 1955 issue of the life insurance medical director's journal, an author calculated the expense to the patient from the day of operation until two or three years thereafter. I do not remember the figure, but it was less expensive than giving rauwolfia, which has proved to be a moderate-priced drug in comparison with some others. Would you not say so, Dr. Perera?

DR. PERERA: Yes.

MODERATOR MASTER: Would you say that the cost might be from ten cents to two dollars per day for antihypertensive drugs?

DR. PERERA: Yes.

MODERATOR MASTER: You have mentioned some of the complications. Would you give an antihypertensive preparation in angina pectoris? That is, in a hypertensive patient with angina pectoris, would the angina pectoris be a contraindication to the treatment of the hypertension?

DR. PERERA: It would not be a contraindication to treatment with rauwolfia preparations.

MODERATOR MASTER: I agree in general, but it would become a contraindication if the blood pressure were reduced too far. Coronary insufficiency might develop.

Have you ever seen arrhythmias or changes in heart rate following the use of rauwolfia preparations? The questioner must have in mind the bradycardia that ensues. Frequently, premature beats will appear. Have you anything to say about this?

DR. PERERA: Aside from bradycardia, I have not seen arrhythmias clearly related to the use of rauwolfia preparations, although extrasystoles have been reported. Increased lactation has been described.

MODERATOR MASTER: Has anyone seen increased lactation with rauwolfia?

DR. FISHBERG: It has been observed, but not by me.

MODERATOR MASTER: Now, we will ask Dr. Moser about *veratrum compounds. What is their mode of action?*

DR. MOSER: Veratrum compounds bring about a fall in blood pressure by vasodilation and a vagal effect upon the heart, produced reflexly from receptors in the heart and lungs. The action is primarily central rather than peripheral.

MODERATOR MASTER: What are some of the veratrum preparations that are commonly employed?

DR. MOSER: We have used none in the last three years. The ones in common use today are protoveratrine and Veriloid, the first being a fairly pure derivative. Our limited experience with this drug three or four years ago showed that, as soon as the dosage approached therapeutic levels, the patient experienced nausea and vomiting or even more severe side-effects. We decided that there were better and less toxic agents to produce a fall in blood pressure, and have not used it since.

MODERATOR MASTER: Dr. Perera mentioned serotonin and that reminded me that lately *antiserotonin preparations have been described. Will you say a word about them*, Dr. Moser?

DR. MOSER: We have had no experience with them. I think Dr. Perera probably has.

MODERATOR MASTER: Dr. Perera?

DR. PERERA: I have. Our experience in a few patients suggests that infrequently a subject responds in a manner similar to that seen after administration of rauwolfia preparations.

MODERATOR MASTER: Dr. Moser, *will you tell us how the hydralazine compounds act?*

DR. MOSER: Hydralazine (Apresoline) is unique in that it probably has several actions, none of which has been clearly defined. For one thing, it blocks

several circulating substances which some observers believe are instrumental in producing hypertension—pherentasin being one. It is also a heavy-metal binding agent. Whether this actually explains its action in hypertension is questionable.

MODERATOR MASTER: Is the action peripheral?

DR. MOSER: There is evidence to suggest that there is some direct peripheral vascular action. Moderate adrenolytic and sympatholytic properties have also been attributed to this compound.

MODERATOR MASTER: Does it affect the hypothalamus? I am asking this for the audience. I should like to have as many associations made as possible.

DR. MOSER: It probably does have some action on the central sympathetic centers in the midbrain. This may be the most important action.

MODERATOR MASTER: Will you give us the dosage?

DR. MOSER: The average effective dosage of hydralazine is usually between 300 and 400 mg. a day, in four fractional doses. The range is much different, some patients responding to 150 mg. a day and others requiring as much as 800 mg.

MODERATOR MASTER: What are some of the complications—those that would be almost classic?

DR. MOSER: Early in the course of treatment, the patient usually experiences either periorbital or ankle edema, transient joint pains, palpitation, and sometimes severe headaches. These symptoms disappear in the majority of cases, if therapy is continued for two to four weeks. They may respond to administration of antihistamine preparations and analgesics. The theory is that hydralazine is an antihistaminase, and by this action it produces histamine-like effects in the patient. These can be combated by the use of any antihistamine preparation. Later on, during the course of treatment with large doses of hydralazine, however, a syndrome that has become fairly well documented occurs in 3 to 5 per cent of patients. It makes its appearance in patients who have received therapy for six months to a year, or more.

This is a rheumatoid syndrome associated with a low-grade fever, joint pains without obvious joint manifestations, occasionally histologic evidence of lupus, and invariably findings suggestive of liver damage. This syndrome is a definite indication for stopping the drug, although some observers continue using it. Symptoms usually disappear within ten days to four weeks, but sometimes it is necessary to use steroid therapy. We have not seen this symptom complex in a single patient since we have been using smaller doses of hydralazine (less than 500 mg. per day).

MODERATOR MASTER: Might the arthritis be a serious complication? You said that steroids would be the treatment. What about lupus?

DR. MOSER: This syndrome is in some way related to diffuse collagen disease, because the symptoms are the same and occasionally histologic preparations show the presence of lupus. I know of only 1 patient, but Dr. Fishberg and Dr. Perera probably know of several more in whom Apresoline therapy was stopped but symptoms continued. I wonder if they would comment on that.

DR. PERERA: I have seen them, too, but it is difficult to establish that these patients did not have systemic lupus initially. In others, the syndrome is more akin to a sensitivity reaction.

MODERATOR MASTER: Is it serious, if this complication develops?

DR. PERERA: To date, it appears to be reversible.

MODERATOR MASTER: Do you mean with the cessation of hydralazine therapy?

DR. PERERA: Yes. May I add to the list of side-effects, psychosis (which we have seen) and depression.

MODERATOR MASTER: That is, with hydralazine. Might there be depression with rauwolfia preparations, too?

DR. PERERA: It is more apt to be a depression. There may be psychoses of different kinds with hydralazine. It is also likely that there is an increased cardiac output after hydralazine, despite claims that the nutrition of the heart is not impaired.

MODERATOR MASTER: Is that in addition to a drop in blood pressure?

DR. PERERA: Yes.

MODERATOR MASTER: Dr. Fishberg, would you like to add anything about the lupus, or the arthritis?

DR. FISHBERG: I have seen 2 cases. Each time it disappeared. I no longer often use Apresoline. Many patients have headaches early in the disease and I am afraid of this other complication. The only antihypertensive drugs I use are rauwolfia and ganglionic blocking agents.

MODERATOR MASTER: That is the next topic.

DR. MOSER: Dr. Master, may I ask Dr. Fishberg whether or not he has seen cases which are well controlled with hydralazine, rauwolfia, and ganglionic blocking agents in combination, and definitely less well controlled when hydralazine is stopped. I ask this because we have had several well documented instances of the hydralazine syndrome developing in patients in whom the hypertension was well controlled; thereafter, when hydralazine was withdrawn, we were unable to bring the hypertension under satisfactory control. Dr. Schroeder has reported similar cases.

DR. FISHBERG: I have had no such experience, because I have never used the 3 together.

MODERATOR MASTER: I, too, have a tendency to use only one drug at a time. However, the reports constantly reiterate that a combination of antihypertensive drugs is usually more efficacious than a single drug.

DR. FISHBERG: I do use 2 drugs, the basic one usually being rauwolfia. I hardly ever use a ganglionic blocking agent without rauwolfia in addition.

MODERATOR MASTER: You do employ *rauwolfia in combination with the ganglionic blocking agents?*

DR. FISHBERG: Yes, but that is when I use a ganglionic blocking agent. I want to make one point about the therapy of what has been called hypertensive crisis, particularly in acute glomerulonephritis and the toxemia of pregnancy. Although we rarely see eclampsia—it disappeared from our hospital because of salt restriction—these antihypertensive drugs are sovereign remedies. For

instance, I have seen amaurosis in acute glomerulonephritis disappear completely and the blood pressure fall with twelve hours after intramuscular injection of Veriloid.

MODERATOR MASTER: With intravenous therapy?

DR. FISHBERG: I almost always use intramuscular injection.

MODERATOR MASTER: What drug preparations specifically?

DR. FISHBERG: It does not matter a great deal. The only one that I use much intravenously is reserpine.

MODERATOR MASTER: I meant which of the ganglionic blocking agents do you employ?

DR. FISHBERG: Of the ganglionic blocking agents, I have never used one intravenously. When we use these agents, it is by subcutaneous injection. I am afraid of the intravenous injection of ganglionic blocking agents.

MODERATOR MASTER: This is so important that I should like the other members of the panel to say a word. Dr. Perera, Dr. Moser, *would you employ drugs intravenously in hypertensive crisis?*

DR. PERERA: True encephalopathy is rarely, if ever, present in primary hypertension, other than in the accelerated form of the disease. If one thinks of the same process in other disorders, then I agree with Dr. Fishberg that acute lowering of the blood pressure may be beneficial. That has been demonstrated by various groups, for example, in toxemia of pregnancy. However, in the case of the "malignant" form of hypertension with encephalopathy, I wonder whether or not there is an analogy with convulsions in children. Sodium restriction, sedation, time, and a few other things are beneficial. These are usually self-limited disorders that respond if one can wait.

MODERATOR MASTER: Dr. Moser, would you like to add to that?

DR. MOSER: This is where I am radical again.

MODERATOR MASTER: We should like to hear about it.

DR. MOSER: We use parenteral agents in patients who are severely ill, with nausea and vomiting, and who are unable to take drugs orally. We used intravenous hexamethonium when that was the first ganglionic blocking agent, and we have used pentolinium (Ansolysen) and mecamylamine (Inversine) parenterally. If intravenous injection is performed cautiously, with careful control, the danger is not too great. The hope of lowering blood pressure to normal levels sometimes carries away the observer, and then the patient may conceivably have a hypotensive reaction. If in lowering pressure we aim for a level of 160 to 170 systolic, there are no serious reactions. I would not hesitate to lower blood pressure in fairly acute fashion in a patient with malignant hypertension and true encephalopathy who was very ill. We have seen some dramatic examples of patients in coma responding quickly to this method.

MODERATOR MASTER: In connection with the use of these drugs intravenously, I heard you mention Inversine. You administer Inversine parenterally, and yet the argument for Inversine is that it is completely absorbed in the gastrointestinal tract. Why do you give it parenterally?

DR. MOSER: The only time we use Inversine parenterally is when a patient is

completely unable to tolerate any medication by mouth. Otherwise, there is no reason to use it parenterally.

MODERATOR MASTER: *Will you please mention some of the contraindications to ganglionic blocking drugs,* Dr. Moser?

DR. MOSER: Dr. Fishberg mentioned the major contraindications a few minutes ago. In a patient with renal insufficiency—not merely impaired urea or P.S.P. clearance, or impaired concentrating ability, but azotemia—the use of ganglionic blocking drugs, or any agents that might lower renal blood flow, is fraught with danger and should be undertaken with great caution. We use ganglionic blocking agents in such patients, but we follow their clearances very carefully. If, within the first week of therapy, we notice a rising creatinine level or a decrease in clearance, we usually reduce the dosage of the drug or discontinue it. Renal insufficiency (azotemia) is one of the major contraindications. The others are a recent myocardial infarction and/or severe angina. In patients with these conditions, the drop in blood pressure may be detrimental. We have never seen coronary occlusion, but we have seen acute coronary insufficiency as a result of lowering the blood pressure.

Another contraindication is a recent cerebrovascular accident. We use these drugs in patients who have had cerebrovascular accidents in the distant past, and we have even employed them in patients who have had recent accidents, if the diastolic blood pressure is very high.

MODERATOR MASTER: I asked for the contraindications and I might logically have asked both Dr. Fishberg and you about them. For example *mecamylamine* (*Inversine*) at this moment is very popular. For what complications should the physician look? Against what should he provide? Will you tell us, Dr. Fishberg?

DR. FISHBERG: Is that about ganglionic blocking drugs?

MODERATOR MASTER: Yes, but Inversine in particular. I chose it because I should like the audience to learn about that preparation. It has become very popular.

DR. FISHBERG: The 2 complications that give the most trouble with ganglionic blocking agents are ileus and hypotensive episodes.

MODERATOR MASTER: What would you do to prevent the ileus?

DR. FISHBERG: Any patient to whom I am administering one of these drugs has an order to take a cathartic every night—usually mineral oil and cascara. Using this plan, there has been no trouble.

MODERATOR MASTER: Do you ever prescribe *neostigmine* (*Prostigmin*) *for treatment or prevention of the constipation*?

DR. FISHBERG: I have given it again and again, but there are people who say that it just reverses the ganglionic blockade. That is not the sensible way to prevent constipation.

MODERATOR MASTER: Do you think that dispensing a cathartic every evening will prevent ileus?

DR. FISHBERG: It has.

MODERATOR MASTER: Do you agree, Dr. Perera?

DR. PERERA: Yes. We try to follow that routine.

MODERATOR MASTER: Have you ever had to employ Prostigmin, for example?

DR. PERERA: It is easier to alter the dosage than to employ counter medications of one kind or another.

MODERATOR MASTER: I think everyone will agree about the cathartic medication, but I have given Prostigmin many times and with success. Dr. Moser, let me inquire again, do you ever give Prostigmin?

DR. MOSER: We use it (along with a laxative) for two reasons: 1) the incidence of urinary retention is much less when using Prostigmin, and 2) although it may reverse the effects of the ganglionic blocking agent on the gut, the blood-pressure response appears to be just as satisfactory with Prostigmin as without it. The only time that it is contraindicated is when the patient cannot tolerate the dose. Sometimes it causes abdominal cramps.

MODERATOR MASTER: It is now time to ask Dr. Smithwick some questions. The first concerns pheochromocytoma. *How would you make the diagnosis of pheochromocytoma?* We used to think that one made the diagnosis on the basis of the paroxysmal nature of the hypertension. Is that true?

DR. SMITHWICK: That certainly is a feature of the diagnosis, of which almost everyone is aware. In paroxysmal forms of hypertension, one automatically thinks of the possibility of pheochromocytoma. I must say, however, that of all the patients I have seen with paroxysmal forms of hypertension, the majority did not have a pheochromocytoma.

MODERATOR MASTER: Now, we shall put it the other way. Dr. Smithwick states that of the patients he has seen with paroxysmal hypertension, the majority did not have pheochromocytoma. Have you any idea how many have a constant blood pressure?

DR. SMITHWICK: Among those upon whom I have operated, which is approximately 30, the majority did not have paroxysmal hypertension.

MODERATOR MASTER: I hope that that impresses the audience. Dr. Smithwick is saying that most patients with pheochromocytoma have constantly elevated blood pressure. Do you agree, Dr. Perera?

DR. PERERA: Yes.

MODERATOR MASTER: Dr. Moser?

DR. MOSER: Dr. Goldenberg is quoted as saying that at least two-thirds have constantly elevated blood pressure. My own experience with 6 patients would appear to bear this out.

MODERATOR MASTER: Dr. Fishberg?

DR. FISHBERG: I think so, at the stage when they have chronic symptoms, but it may be that a higher proportion start with paroxysmal hypertension.

MODERATOR MASTER: In any case, there is a difference of opinion, as there should be, about the percentage. We agree that when the hypertension is paroxysmal, it may help one to make the diagnosis. However, it may not be paroxysmal; it may be constant. Dr. Moser quoted Dr. Goldenberg, who said that two-thirds of these patients have a constant blood pressure. To repeat, we are speaking of pheochromocytoma.

Dr. Smithwick, will you give us an idea how frequent it is. Are the practicing

physicians in the audience likely to observe a pheochromocytoma in their lifetimes?

DR. SMITHWICK: According to my statistics, the incidence is about 0.5 per cent. This is based largely upon patients who have been operated on, because unless one operates on the patient and actually explores the adrenals, many pheochromocytomas will be missed. As a matter of fact, at least half of those that we have found over the years were found unexpectedly at the time of operation. Today, that is less likely because of the simple urine tests that can be used with fair accuracy to screen these patients.

MODERATOR MASTER: *Would you use the catechol-amine urine test? To the exclusion of the methanesulfonate (Regitine), benzodioxane, and histamine tests?*

DR. SMITHWICK: It is a much more satisfactory test, when there is any real reason to use it. One ought to pay great attention to the signs and symptoms of the disease. If the 10 most common ones are kept in mind, the physician probably will not overlook many cases. Any patient who has 1 of the 10 signs or symptoms along with hypertension should be screened, preferably by a urine test, because drugs that lower blood pressure or precipitate attacks in these patients are dangerous and may yield false positive results.

MODERATOR MASTER: Dr. Smithwick, do you think that physicians ought to test all hypertensive patients for pheochromocytoma?

DR. SMITHWICK: I do not believe that would be practical, but I think that every physician should give careful attention to the common signs and symptoms.

MODERATOR MASTER: Do you think they should do that only when there is an indication?

DR. SMITHWICK: One ought always to keep the possibility in mind and be alert to the fact that, regardless of the form of hypertension, the patient can have pheochromocytoma if he has certain signs and symptoms.

You mentioned the histamine and Regitine tests. The hazards of the tests themselves are very real, and neither one should be used as a routine screening measure. I would not think of using them until I had performed a urine test.

MODERATOR MASTER: Does anyone want to add anything? Dr. Fishberg, do you want to add to what Dr. Smithwick has said?

DR. FISHBERG: I agree with Dr. Smithwick, but one difficulty is in carrying out the urine test. It is performed in only a few places. Moreover, there appears to be less pheochromocytoma than there was a few years ago. In the last three or four years, I have seen only 2 cases.

MODERATOR MASTER: Dr. Perera, have you a word concerning pheochromocytoma?

DR. PERERA: No. I agree with what has been said. It is a rare condition. There is no need to screen every patient. However, if there is the slightest clue such as a paroxysmal tendency, abnormal sweating, transient glycosuria, or hypermetabolism, then a screening procedure is worthwhile.

MODERATOR MASTER: Does that hold true in hospital practice, too? We have already agreed that there is no need to perform the tests unless there are signs and symptoms suggesting the possibility of a pheochromocytoma. What about a hospital?

DR. PERERA: It is a matter of point of view. If we were being ideal, we would examine everything in everybody. Being practical, routine screening is not employed in most hospitals.

MODERATOR MASTER: I asked that question because I have heard Dr. Moser say that his group screens everyone for pheochromocytoma.

DR. MOSER: Yes, we do.

MODERATOR MASTER: Will you tell us about it.

DR. MOSER: We do it in 2 ways. In patients with constant hypertension, we use the Regitine test. If the findings are positive, we go further, because there are many false positive results. We have seen no untoward consequences of this test. One accident has been reported in the literature, but the only symptoms our patients have experienced are tachycardia and flushing. We also use a rapid urine test for catechols, which Dr. Goldenberg has assured us will screen out typical pheochromocytoma. Although it is not as accurate as his procedure, which is long and complicated and requires an expert technician, we have been using it as a screening test. Although one certainly does not see many pheochromocytomas, I think it worthwhile to perform a Regitine test. We all perform urea clearances on our hypertensive patients and no one has ever been cured as a result of this procedure. The Regitine test takes less time and does not put the patient to any risk; in rare instances it may even result in a cure.

In the normotensive phase of labile hypertension, we use the histamine test. This is *not* a simple innocuous procedure and must be performed with caution. A positive result usually indicates a pheochromocytoma.

MODERATOR MASTER: Is this in the hospital?

DR. MOSER: Generally yes, in the hospital.

MODERATOR MASTER: You do not perform this test in your office, do you?

DR. MOSER: I do, but it is not a customary office procedure.

MODERATOR MASTER: Do you look for pheochromocytoma in all your patients, even though they may not have the clinical syndrome that Dr. Perera pictured?

DR. MOSER: I still do, but I may lose my energy some day.

MODERATOR MASTER: While you were speaking of the catechols, I recalled that recently I read a paper in which the statement was made that tense situations may cause measurable amounts of catechols to appear in the urine. Is it possible that Dr. Goldenberg, finding catechols in the urine, might make a mistake and diagnose pheochromocytoma when their appearance was due to emotion?

DR. MOSER: According to Dr. Goldenberg—and this is the only wide experience I can quote, although Swedish investigators have made some studies—he has an initial rapid screening test which can determine up to about 100 micrograms of catechols in the urine. He tells me that a patient with anxiety, an infarction, or any one of the things that might produce emotional reactions, will excrete more epinephrine than the normal person. However, I believe that it has not been his experience so far that these levels of excretion have approached the level in pheochromocytoma. Thus, although catechols may be detected in the

urine in this first screening, in the second screening the results usually enable him to differentiate between the 2 clinical conditions.

MODERATOR MASTER: We shall turn again to Dr. Smithwick. *Is it true, as some say, that surgery no longer has a place in the treatment of hypertension?*

DR. SMITHWICK: I have not heard that.

MODERATOR MASTER: Dr. Smithwick, please tell us the place of surgery in hypertension.

DR. SMITHWICK: In our experience, it has been most valuable in patients having the more severe forms of the disease with significant cardiovascular changes that ordinarily carry serious implications, *i.e.*, up to the point where no form of therapy will be of avail. This involves particularly the state of the kidney. Once a patient has persistent nitrogen retention, the situation is hopeless, and he certainly should not undergo operation. Also when heart disease is extensive—especially when associated with marked diminution of renal function, even though there is no azotemia—it is open to question whether a patient should undergo surgery. If a patient has advanced cerebral deterioration or has had a cerebrovascular accident that is highly crippling, he probably should not be operated upon for hypertension.

MODERATOR MASTER: Should not?

DR. SMITHWICK: He should not. In the early stage of hypertension before vascular disease appears, medical therapy is indicated. If for one reason or another medical treatment is unsatisfactory—the patient is hard to handle and cannot be followed, or his manner of living is such that he either cannot or will not adhere to a satisfactory medical regimen—it is proper to operate earlier in the disease.

This applies particularly to male patients. As a matter of fact, I will go even farther than that. The mortality rate and prognosis are so much worse for young males aged 30 to 40 years with severe hypertension that serious consideration should be given to operation before cardiovascular disease occurs.

MODERATOR MASTER: Dr. Smithwick is being entirely too modest. I had a patient, a physician aged 45 years, on whom Dr. Smithwick operated many years ago. Before operation this man had had unbelievably high blood pressure, a huge heart, heart failure, retinal changes, and electrocardiographic abnormalities. Since operation he has remained very well. He used to come in regularly, but I have not seen him professionally for at least five years. However, I do see him every day at the hospital. He is extremely active—much more active than even the average doctor. The Smithwick operation has been phenomenally successful, in this instance.

Dr. Fishberg, you have many cases. Do you want to tell us about them? I shall come back to Dr. Smithwick.

DR. FISHBERG: Without doubt, hundreds of persons in the United States are alive today because of sympathectomy—Dr. Smithwick's operation. Again and again, I have seen definite prolongation of life. I have also seen patients who, though not completely cured of hypertension, have fared well for many years; there is every reason to believe they would not have done so without sympathectomy. Since the introduction in the last few years of systematic salt restric-

tion and hypotensive drugs (which constitute a clumsy and hard-to-apply medical sympathectomy), the number of hypertensive patients in whom surgical sympathectomy is indicated has been greatly reduced. In a small proportion of patients, sympathectomy is still indicated, but it is not easy nowadays to persuade them to undergo operation. The year 1956 is coming to a close; during it, we performed not a single sympathectomy in our hospital. I advised 2 people to have the operation, but they did not consent to it. I think the pendulum has swung too far. It will have to be realized that there are some patients in whom sympathectomy still is indicated.

MODERATOR MASTER: Dr. Perera and Dr. Moser, would you like to say a word about this before I return to Dr. Smithwick.

DR. PERERA: In the accelerated form of the hypertension, before there is much nitrogen retention, I would definitely recommend sympathectomy in preference to antihypertensive drugs. Once performed, one can still use drugs, if necessary. It is a finite procedure, and is relatively safe. Dr. Smithwick's experience is supported by that of many other groups, in that there is a clear-cut lengthening of life in a certain percentage of patients—perhaps 30 or 40 per cent of those in the stage of the disease involved. I agree that there is an occasional place for sympathectomy in the young patient, when one judges on clinical grounds that the hypertension is going to pass into the accelerated form. I would still raise a question as to the value of sympathectomy, as regards life expectancy, in earlier stages than the accelerated form of the disease.

MODERATOR MASTER: Dr. Moser?

DR. MOSER: I have nothing to add.

MODERATOR MASTER: I think we all agree that Dr. Smithwick's contribution is of high caliber. Now that we have all said that, I am going to ask Dr. Smithwick *what are some of the complications and difficulties following sympathectomy.*

DR. SMITHWICK: If a sympathectomy is of the proper order of magnitude, few complications or difficulties are worth mentioning in comparison with the benefit the patient obtains and the greater ease with which he is handled, if he has a serious form of hypertension with significant cardiovascular changes that are not too advanced. With reference to the accelerated phase of the disease that Dr. Perera and Dr. Fishberg mentioned, some cases progress rapidly as far as demonstrable changes in the cardiovascular system are concerned. Even if the hypertension is not in a rapidly progressive phase, but there is a certain amount of significant cardiovascular disease, the patients will benefit a great deal from sympathectomy, not only with regard to life expectancy (statistically) but also with regard to slowing of the progression of the hypertension.

An unfortunate thing about the operation for hypertension is the difficulty in performing it. In my experience over the years, it probably has been harder for surgical residents to learn how to perform this operation properly than any other operation in surgery. It is an unusual area of the body, and the exposure is difficult unless one has had a great deal of experience with it. It is not an operation that can be performed generally in a widespread manner throughout the United States.

MODERATOR MASTER: What about possible hypotension?

DR. SMITHWICK: That depends entirely upon the magnitude of the operation. As you know, in the years of its development, operations ranged from those of minor magnitude up to total sympathectomy. If a total sympathectomy is performed, serious postoperative trouble may last as long as five years. That is why I say that the operation should not exceed a certain extent. When the operation is of the proper kind, postural hypotension is of no consequence. It does not last in any appreciable degree for longer than two months, as a rule. There are other physiologic changes, such as cold hands in winter and excessive perspiration in the summer (because of the denervated areas), but they are rarely troublesome and tend to lessen with the passage of time so that, after two or three years, patients do not notice them.

As for immediate disability, the period of hospitalization is much shorter than it used to be. During the last five years, we have performed all of the operations in one stage. Previously, we operated on one side, and ten days later on the other side. Now, we can handle both sides at one time without increasing morbidity or mortality. That is something that few surgeons can accomplish, because it requires tremendous experience with the procedure and a highly organized team. Otherwise, I am sure the morbidity and the mortality would be prohibitive. The hospital stay now is usually about two and a half weeks.

MODERATOR MASTER: I should like to turn to other surgical procedures. *Is denervation of the carotid sinuses of value as a form of antihypertensive therapy?*

DR. SMITHWICK: No, that procedure has no value. In combination with section of the aortic depressor nerves, it is the best way that I know of to produce the neurogenic form of experimental hypertension.

MODERATOR MASTER: *What can you say about complete adrenalectomy?*

DR. SMITHWICK: I am sure that an occasional patient has some abnormality of function of the adrenal cortex which has a great deal to do with his hypertension. However, we do not know how to find these patients, except the rare one with hyperaldosteronism, in which condition the potassium levels are extremely low. Every now and then we find a case—usually a cortical adenoma. I am sure that partial bilateral adrenalectomy is of no value, but occasionally complete adrenalectomy may be helpful. We never perform this operation, except as a last resort in a patient who has proved completely refractory to splanchnicectomy combined with restriction of sodium and the best possible therapeutic program with drugs. If he still has severe hypertension, is in good shape, and especially if he is young, we perform a total adrenalectomy. Nothing less than that is worthwhile.

MODERATOR MASTER: Dr. Smithwick, *given a patient with hypertension, whose intravenous pyelogram reveals a large cyst in one kidney, would you recommend surgical removal of the cyst?*

DR. SMITHWICK: I am sure it would do no good as far as hypertension is concerned. The answer to that is the same as Dr. Fishberg's answer as to when to consult a psychiatrist.

MODERATOR MASTER: As we have actually answered 80 to 90 per cent of the

questions that we had intended to cover, I shall take a few minutes to answer some questions that have been directed to me.

What is the distinction between "basal" and "casual" blood pressures? "Casual" pressure is the ordinary blood pressure. It is the blood pressure that we all should deal with, since all people are constantly exposed to the stress and strain of life. It is true that when you take a blood pressure in your office, you should have a matter-of-fact atmosphere, and the patient should rest a bit; but that is still the "casual" blood pressure. "Basal" pressure is the arterial pressure of someone who has been put to bed for days or weeks, and even then only after he has received barbiturates and other drugs.

Why do women have a higher incidence of hypertension? Only God knows! They live longer. I don't know why they have more hypertension, but after the menopause their blood pressure normally is higher than that of men.

If hypertension is associated with arteriosclerosis, why does not more arteriosclerotic heart disease develop in women? We do not know. The answer is complicated. There may be some relation to the blood levels of cholesterol and lipoproteins. As most of you know, we are now obtaining blood pressure readings of people 65 to 100 years of age and over. Women still maintain a higher blood pressure to the age of 100 years.

What is the relation of hypertension to atherosclerosis, coronary occlusion, gout, and diabetes? There is a definite relation to arteriosclerosis. Hypertension apparently accelerates arteriosclerosis and yet, at times, hypertension seems to help. Again and again, one sees a patient with a distinctly elevated blood pressure whose electrocardiogram (resting) is normal and in whom even the two-step test yields normal findings. However, there finally comes a time when chest pain develops. From this point on, complications may develop sooner than otherwise, in a hypertensive patient.

Does hypertension cause coronary occlusion? I believe that hypertension is a factor in women, but not in men.

I do not know about gout. In the classical form, it is hardly seen these days. Was it once thought that hypertension was related to gout? Dr. Perera, do you think there is any relation between them?

DR. PERERA: Not clearly. If there is a relation, it is more likely a common genetic factor rather than a relation of one disorder to the other.

MODERATOR MASTER: The blood pressure in mitral stenosis is another question. Sam Levine believed that the incidence of hypertension among patients with mitral stenosis was higher than among other people, but it has not been proved.

Why does not the blood pressure of normal people after 70 years of age continue to rise? That question arose from the fact that our studies of blood pressure in apparently healthy people more than 65 years old (range, through age 106) indicate that there is a difference in the average level from that of younger persons. From birth to age 65, the blood pressure increases steadily with age. At age 70, however, because of some biologic event, the blood pressure no longer rises. The explanation that occurs to us is that those patients who have either

hypertension or a high "normal" pressure probably do not survive to a very old age.

Are life insurance companies planning to alter their blood-pressure standards in the light of your findings? That question is a great compliment to me. I always say that our observations have had nothing to do with life insurance companies. Their standards are based on business return, whereas we try to interpret our blood-pressure readings from a clinical point of view. That the insurance companies are, nevertheless, interested in our results is shown by the fact that I receive requests for our tables from many of them. Life insurance medical directors often write that they are distributing our tables to their examiners, so apparently some of the companies have decided to make their limits of normal blood pressure more liberal.

Can an insurance company detect an applicant's use of an antihypertensive drug? I should think that would be a real problem to life insurance companies, and I have been told that they cannot. Have you any idea about this point, Dr. Perera?

DR. PERERA: No, I have not.

MODERATOR MASTER: Dr. Fishberg?

DR. FISHBERG: If one saw a hypertensive patient with a heart rate around 55 or so, he might wonder.

MODERATOR MASTER: In other words, you would be suspicious.

Has coronary occlusion been precipitated by the use of hydralazine or the ganglionic blocking agents? I have never seen coronary occlusion but I have seen acute attacks of coronary insufficiency. These were caused by significant falls in blood pressure.

DR. PERERA: We have had 3 instances of myocardial infarction that occurred in association with reductions in blood pressure due to ganglionic blocking agents. It is enough to make one hesitant.

MODERATOR MASTER: I see Dr. Howard Sprague in the audience, awaiting his panel. We should like to hear from you, Dr. Sprague.

DR. SPRAGUE: I do not know whether it is fair for one panel to ask another panel a question, but it seems to me that one form of hypertension belongs in the hands of the surgeon. That is *the hypertension associated with unilateral renal disease*, which has not been mentioned.

MODERATOR MASTER: Dr. Fishberg?

DR. FISHBERG: Unilateral? Under what circumstances, Dr. Sprague?

DR. SPRAGUE: One should suspect the presence of unilateral renal disease (on an arterial basis) if there is malignant hypertension in a person under the age of 35 years, or if hypertension appears following pain in the flank. Apparently, it has been possible by aortography to demonstrate these lesions, and to cure them by surgery. Have you had any such experience?

MODERATOR MASTER: Anyone? Dr. Perera?

DR. PERERA: No. Most unilateral renal disease, however, does not cause hypertension. In the few instances in which the blood pressure is elevated, it can be lowered by removal of the kidney. It has been our experience that in the

majority of these patients, given time, the hypertension will follow an accelerated course. In almost every instance in which severe hypertension has appeared for the first time after the age of 50 years, we have found it to be other than a primary disorder. In other words, the sudden appearance of severe hypertension in older people should make one look hard for a reversible, or a secondary cause.

MODERATOR MASTER: Dr. Smithwick was eager to reply to Dr. Sprague.

DR. SMITHWICK: Dr. Sprague has very properly raised this question. Those carrying out studies of one kind or another seem to think that they are able, by radioactive iodine clearances and other means, to detect unilateral renal disease more accurately than we were able to do in the past. Arteriosclerosis may be present, or a renal artery may be blocked. Such blocking is being discovered more frequently than it was years ago, especially since arteriography is being performed much more commonly in connection with peripheral vascular disorders. Thus, quite a few patients have been found to have hypertension on this basis and have been relieved by direct surgery on the renal artery.

For the most part, we are probably talking about the effects of arteriosclerosis in older age groups. I have operated on perhaps 3,000 hypertensive patients, and the interesting thing to me is that the average age of the whole group is 45 years. By and large, these patients are young; the percentage over age 50 is very small. Perhaps the cases being discovered today are, for the most part, in older persons with arteriosclerosis.

Each one of our 3,000 patients had an intravenous pyelogram; the renal arteries were carefully palpated from the aorta out, the kidneys were carefully explored, and renal biopsy specimens were taken. I found only 2 patients with hypertension due to unilateral renal disease, and they were in the younger age group.

A COMMON MOLECULAR BASIS FOR THE AGING SYNDROME

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The manifestations of aging are many, but there are certain underlying phenomena which they have in common.

The clinical symptoms of degenerative diseases are well known, and by the use of histologic techniques definite microscopic changes have been found. The chemical processes underlying these changes have not been properly elucidated, however. With advancing age, there is a slowing in metabolism, a loss of elasticity of the tissues, an increasing brittleness in bone and cartilage, a loss of water-binding capacity, and above all, a reduced resistance to disease and to trauma of all kinds.

This reduced resistance is represented graphically in Figure 1. The curve is based on the mortality rate for the total U. S. population (1).

In the exploration of possible causes for the progressive changes in body tissues which take place in aging, it appeared that certain of these might be interpreted in terms of polymer chemistry, especially with reference to known reactions of protein-type polymers. Reactions which result in exponentially progressive phenomena similar to those observed in the aging syndrome are found in the cross-linkage of proteins, and other reactions capable of changing their solubility characteristics and susceptibility to enzymatic hydrolysis. It appeared pertinent therefore to note reported evidence in the literature of the presence in the bloodstream of substances capable of causing changes in proteins, which *in vitro* in protein gels closely parallel the changes in elasticity, brittleness and water retention observed *in vivo* in senescent tissues. A search disclosed numerous well-documented reports of the presence in normal blood of substances which can cause aggregation or insolubilization of protein molecules by cross-linkage (Table 1).

CROSS-LINKAGE OF PROTEINS AND RESISTANCE TO ENZYMATIC HYDROLYSIS

A cross-linkage results when a molecule with 2 or more reactive groups reacts with one protein molecule at one of these groups and with another protein molecule at another reactive group. The result is the formation of a new molecule, the molecular weight of which is the sum of the molecular weights of the 2 component protein molecules, and the molecular weight of the cross-linking agent. From these data it appears that in the bloodstream there are enough cross-linking agents to cause progressive cross-linkage of some of the protein, and possibly also to enhance the oleophilic properties of protein materials in the tissues (19).

In view of the relative abundance of potential cross-linking constituents in human blood (Table 1), as well as the known cross-linking influence of ubiquitous ionizing radiation (20, 21, 22), it appeared of interest to explore the reason

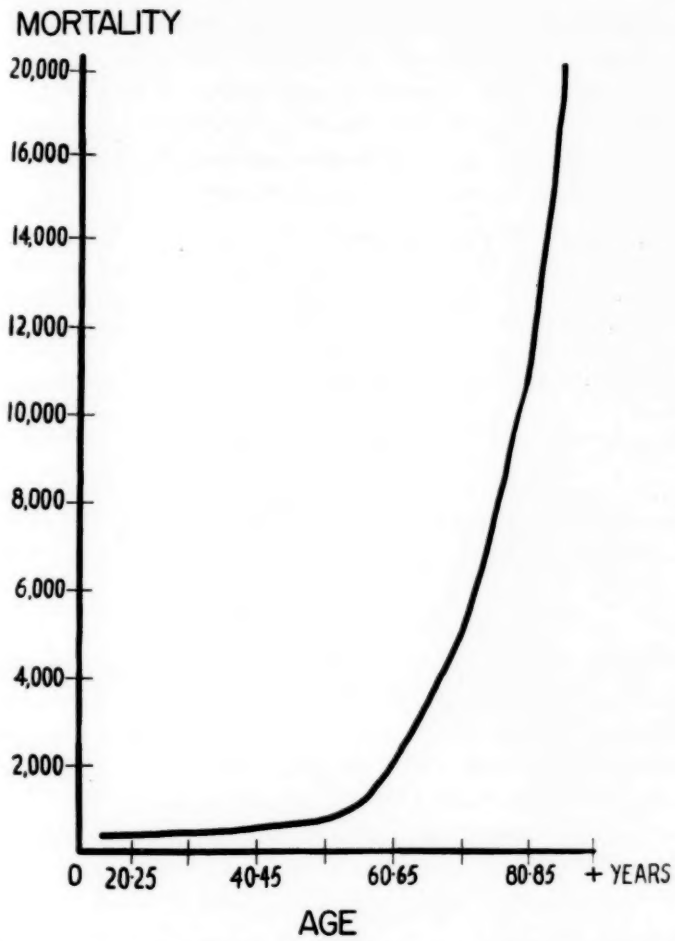

FIG. 1. Reduced resistance (mortality rate) with advancing age.

why these influences do not cause loss of elasticity and embrittlement in human tissues considerably more rapidly than is the case in normal aging. We have to assume that a defensive mechanism exists. The nature of this defense mechanism against progressive cross-linkage of proteins is suggested particularly by the work of Schoenheimer (23), Baldwin (24) and others, who have investigated the dynamic state of proteins in the body.

It was shown by these researchers, that protein molecules are continually broken down and re-synthesized.

The turnover is different for different tissues; the general range of half-lives is 5–200 days, with 80 days a general average for adult humans. Until recently it was thought that the proteins in the brain were metabolized slowly, but recent studies by Bakay (25, 26) have shown that this conclusion depended on failure to allow for the time necessary for passage of tagged amino acids through the blood-brain barrier, and that when the tracer substances are injected directly into the brain, there is a rapid rate of turnover. When a protein is broken down

TABLE 1. *Potential Cross-Linking Agents in Blood*

Agent	Concentration
Acetaldehyde (2)*	<0.1 mg./100 cc.
Methyl guanidine (3)	0.2–0.3 mg./100 cc.
Alpha ketoglutaric acid (4, 5)	0.2–0.9 mg./100 cc.
Pyruvic acid (6)	0.4–2.04 mg./100 cc.
Alpha keto acids, only generically identified (7, 8)	0–3.1 mg./100 cc.
Citric acid (9, 10)	1.3–6.0 mg./100 cc.
Malic acid (11)	0.1–0.9 mg./100 cc.
Fumaric acid, in rat (12)	<0.3 mg./100 cc.
Succinic acid (13)	0.5 mg./100 cc.
Silicon (14)	33–63 μg./100 cc.
Lead (15)	18–49 μg./100 cc.
Aluminum (15)	15–40 μg./100 cc.
Copper (16)	73–115 μg./100 cc.
Iron (17)	43–52 μg./100 cc.
Manganese (15)	0–25 μg./100 cc.
Zinc (18)	488–1272 μg./100 cc.

* Reference number.

to polypeptides and component amino acids, cross-linkages are dislodged; and when the protein is resynthesized, it is synthesized in its original state, since the synthesizing mechanism obviously would not replace the cross-linkages. If this defense mechanism functioned with complete efficiency, it appears that protein immobilization and its subsequent effects would be prevented. However, in this enzymatic mechanism there is an inherent imperfection, which, should it not suffice to explain the primary processes of aging, at least could account for phenomena which theoretically would result in changes similar to some changes observed in aging.

It is well known that proteolytic enzymes attack protein molecules at certain points. Assuming that molecules of cross-linking agents should block all the points of attack on 2 adjacent cross-linked protein molecules, then these protein molecules could not be broken down by the body enzymes, and they would remain immobilized. Since cross-linkage is a random process, dependent on chance contacts between the cross-linking agents shown to be present in the blood and the reactive groups in the protein molecules, it is apparent that in a certain statistically ascertainable percentage of such contacts the points of the molecules where body enzymes can attack will be blocked, and that the proteins thus blocked become fixed and immobile, and effectively withdrawn from participation in any metabolic reactions. As chronologic age progresses, an increasing amount of protein is thus made inert; it tends to clog the cells, interfering first slightly, then at an increasing rate, with the normal functions of the cell.

EXPERIMENTAL DATA

An important point in this theory, which is susceptible to experimental verification is:

Does cross-linkage of proteins in fact interfere with hydrolysis by enzymes, as postulated? This point was checked by cross-linkage of gelatin with known cross-linking agents, and subsequent treatment with a series of proteolytic enzymes. Yields and identity of liberated amino acids were studied by paper chromatography. It was shown that a portion of the cross-linked protein actually is made inaccessible to enzymatic action by pepsin, trypsin, papain and ficin (27, 28).

Figures 2 and 3 illustrate the data on which this conclusion is based. These data are taken from a report to the Office of Scientific Research of the U. S. Air Force, presented by Bjorksten and Gottlieb (29).

To a 5 per cent aqueous solution of 375 Bloom pig-skin gelatin was added formaldehyde in the molar ratios shown below Figure 1.

After forty-eight hours, the amino acids were determined by a paper chromatographic method.

Six-ml. aliquots of the reaction solutions were spotted on Whatman #1 chromatography paper. Reference spots of known amino acids were added to each strip before development. The developments were continued for approximately twenty hours in 4:1 (W/V) phenol-

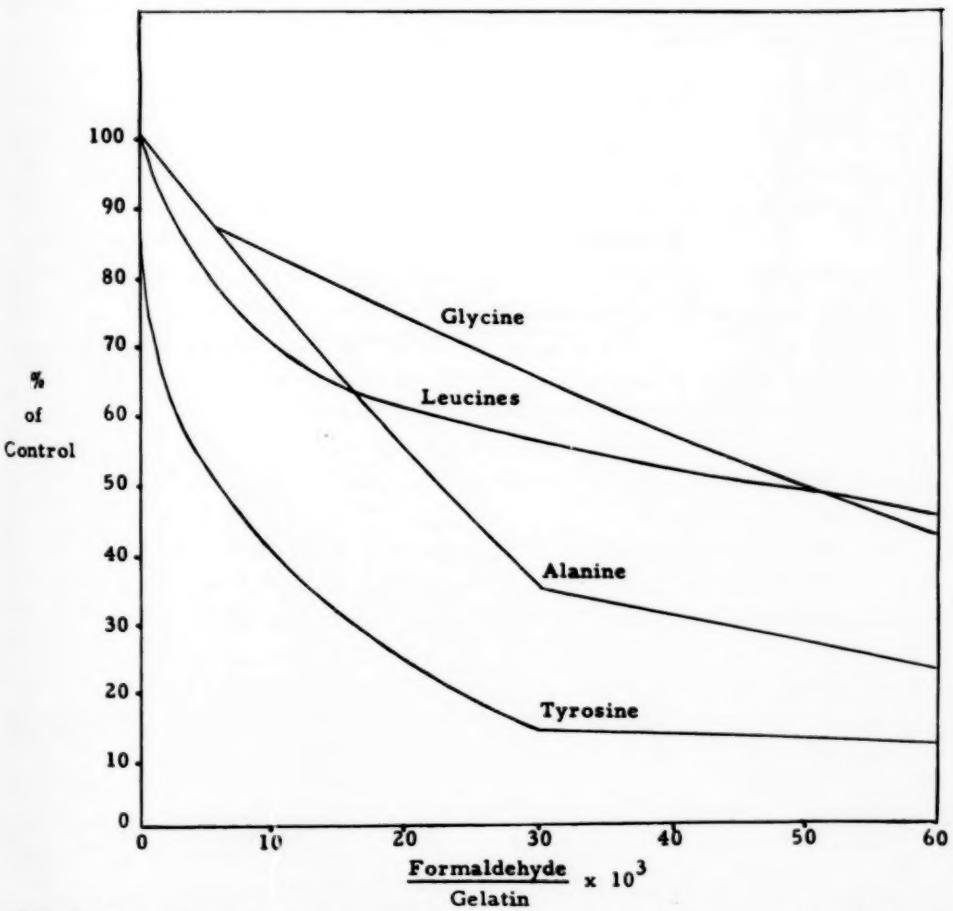

FIG. 2. The amino acids of formaldehyde-treated gelatin after 48-hour hydrolysis with trypsin.

water, 4:1:1 (V/V/V) butanol-water-acetic acid and 75:35:25 (V/V/V) methyl ethyl ketone-water-propionic acid at room temperature.

After development, the strips were air dried and sprayed with 0.25 per cent Ninhydrin in water-saturated butanol. The color reaction was allowed to continue several days at room temperature before carrying out qualitative and quantitative evaluations of the amino acids. The measurements were made by careful visual inspection at the height of the color intensities. The discernible spots were graded on a six-point intensity scale. The color scores for the amino acids from the untreated gelatin were used as the standards. The coloration produced by the amino acids from treated gelatin was scored as the percentage of the corresponding coloration produced by the amino acids from untreated gelatin after correcting for the coloration from the reagent controls for each of the hydrolytic reagents.

Figure 2 shows that the proteins are affected by the cross-linking process in such a way that trypsin no longer can release more than a portion of the amino acids normally hydrolyzable, and that the amount which can be released is greater for glycine and leucine than for alanine and tyrosine.

Figure 3 shows the degree the refractoriness of protein to trypsin hydrolysis when para-benzoquinone is used as the cross-linking agent instead of formaldehyde. The procedure was the same as in the preceding experiment.

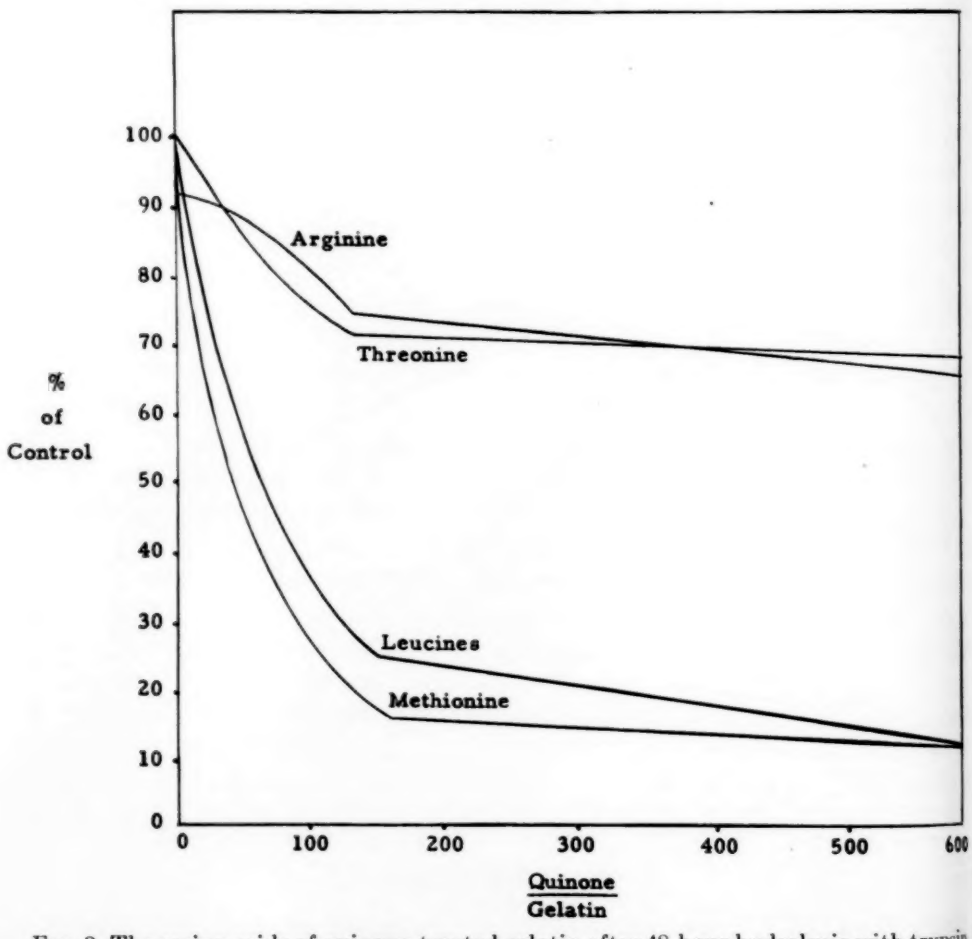

FIG. 3. The amino acids of quinone-treated gelatin after 48-hour hydrolysis with trypsin. The values on the abscissa are the molar ratios of quinone/gelatin.

Hundreds of determinations have been made and are being published separately (29). The results are substantially similar when different protein substrates, proteolytic enzymes and cross-linking agents are used. The foregoing data, however, should suffice to show that progressive cross-linking does indeed render a protein progressively resistant to enzymatic hydrolysis.

IMMOBILIZATION OF PROTEINS AS A BASIC CAUSE OF AGING

Other effects obtainable by cross-linkage may be related to phenomena of aging. As discussed in previous publications (19, 30), arterial tissues exposed to several known cross-linking agents become oleophilic; this may have some bearing on interaction between fatty material (including cholesterol) and arterial surfaces. Also, the progressive loss of elasticity of certain tissues exposed to continuous pulsation (31) may be caused by cross-linkage and may in turn result in minute ruptures which initiate further damage.

In the years preceding the first publication in which the working hypothesis of immobilization of proteins as the basic cause of aging was stated (32), observations had been brought forth which were compatible with this hypothesis. It may be pertinent to review supporting observations:

1) Loss of elasticity in many body tissues is a characteristic of old age. Loss of elasticity is a characteristic effect of cross-linking.

2) Increased brittleness of rigid tissues is a characteristic of old age. Increased brittleness is a characteristic effect of cross-linking.

3) Decline of the percentage of bound water is a characteristic of old age. Decline of the percentage of bound water is a result of cross-linking in water binding proteins.

4) Diabetics are particularly susceptible to degenerative circulatory disease. Diabetics have what is known as a ketogenic metabolism, most likely to give rise to potential cross-linking agents in the organism.

5) Animals receiving very low caloric diets have a substantially increased life span (33, 34). A very low caloric diet makes for a minimum of metabolic by-products which might act as cross-linking agents.

6) Aluminum, a potent cross-linking ion, accumulates progressively with age in tissues of dogs (35).

In the sixteen years since this working hypothesis was first reported, it has been elaborated and further developed (36, 37). Observations in several laboratories have produced the following experimental evidence which is compatible with the hypothesis:

1) Ionizing radiations, known to cause cross-linking of large molecules (20–22, 38–40), also cause symptoms resembling those of natural aging (41–45).

2) On aging, a large aggregate protein substance accumulates in the arteries progressively (46).

3) On aging, aluminum, a potential cross-linking ion, accumulates concurrently with a protein material in arterial tissues (47).

4) Accumulation of mucoprotein takes place in tissues with aging (48).

5) In a certain unicellular organism, the macronucleus increases greatly in size with age, indicating compensation for immobilization of proteins; and a

concurrent precipitation of organized protein is visible in the electron microscope (49).

6) These "chromatin bodies" appear earlier, in Tokophrya organisms in which the life span has been shortened by overfeeding (50–53).

7) On aging, colloidal material, presumably of protein nature, accumulates in kidneys (54).

Further supporting evidence:

1) Chemical cross-linking agents alter the hydrolysis of proteins by body enzymes (19, 27, 28, 30).

2) Proteins irradiated to the point of altered aggregation exhibit alterations of proteolysis by enzymes (28).

3) By treatment with certain cross-linking agents, arterial walls can be made absorbent for cholesterol or any other lipids (19, 30).

How the immobilization of proteins occurs, and its relationship to aging are subjects for further study. At present, cross-linkage seems to us the most likely mechanism. However, polymerization of proteins without cross-linking, denaturation or crystallization could also be the cause of immobilization and contribute to withdrawal of proteins from their normal functions.

The next phase of the study should be directed to obtaining more specific knowledge of the reaction which leads to the immobilization of proteins. When this information is available, specific controls and counter-measures may become possible. For example, if a certain type of cross-linkage should be found to account for a large part of the aging syndrome, a search for suitable enzymes or agents capable of breaking that cross-linkage would be indicated.

For a frontal attack on the problem, increased efforts and funds are needed. As pointed out by E. V. Cowdry (55), studies directed toward the fundamental chemistry of aging on a molecular level are likely to prove rewarding in the elimination of degenerative diseases, as they would strike directly at the cause of these diseases.

SUMMARY

Degenerative changes must have a basic cause on the molecular level. For example, the possible role of protein immobilization by means of progressive cross-linking reactions is critically examined in the light of known data on potential cross-linking agents present in the blood stream, and of related physiologic facts.

Acknowledgment

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TREATMENT OF ACUTE AND CHRONIC ARTHRALGIAS WITH A TRANQUILIZING AGENT (TRILAFON) IN ADDITION TO PREDNISONE OR PREDNISOLONE

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A comprehensive approach to the treatment of arthralgia, whether of traumatic or inflammatory origin, requires awareness of the role played by anxiety and apprehension. Fear of pain often exaggerates the functional limitation of motion far beyond that attributable to organic involvement. Nervousness and apprehension also intensify painful spasm of the voluntary muscles. Lack of sleep, resentment of dependency, and fear of loss of earning capacity are typical psychic stress factors which enhance the primary disorder and prolong disability.

Therefore, in the treatment of disorders of the joints, supplementation of basic adrenal steroid therapy with an effective tranquilizing agent is a rational therapeutic approach. The aim is to speed recovery by treating both the organic factors and the complicating emotional component.

MATERIALS AND METHOD

The materials used in this study were prednisone (Meticorten), prednisolone (Meticortelone) and perphenazine (Trilafon).[1] The adrenal steroids are used extensively, with notable success, to treat various types of arthritis and soft-tissue rheumatism (1–7). Trilafon is an ataractic drug, in the phenothiazine class, which has proved extremely useful in a wide range of emotional problems (8–14).

Two groups of patients were selected. Group A consisted of 21 ambulatory middle-aged patients with acute and subacute disorders of the joints, chiefly of traumatic origin. Group B consisted of 29 elderly patients in a geriatric rehabilitation center, who had chronic articular disorders of inflammatory or nutritional origin. The common denominators were severe pain in the joints and muscle spasm. The diagnoses in both groups are summarized in Table 1.

We wished to evaluate varying dosage schedules of Meticorten (and Meticortelone) with Trilafon in order to find the optimal levels at which symptoms would be relieved with a minimum of side-effects. One tablet with 2.5 mg. or 5 mg. of either steroid was administered three or four times daily along with a tablet containing 2, 4, or 8 mg. of Trilafon. The combinations and their distribution among the patients are shown in Table 2.

Initially the higher dosages of both drugs were used; if no response was obtained within three or four weeks the case was considered a failure. When a good response—as judged by disappearance of pain, spasm, swelling and immobilization—occurred within two weeks, lower dosages were administered. Dosage was also reduced if side-effects appeared. Gradually the minimum maintenance dosage for each patient was determined.

RESULTS

Optimal dosage; relation to age of subject

Group A (21 ambulatory middle-aged subjects). Meticorten (5 mg.) and Trilafon (8 mg.) three or four times daily, proved markedly effective in all of the 14

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[1] These agents were provided by George Babcock, Jr., M.D., Division of Clinical Research, Schering Corporation, Bloomfield, N. J.

TABLE 1. *Diagnoses*

Group A	
(Ambulatory patients aged 34–59 years)	
Acute traumatic low-back syndrome	10
Recurrent bursitis, pericapsulitis	6
Acute traumatic arthritides	2
Acute and subacute myositis and tendinitis	3
Total	21
Group B	
(Hospitalized patients aged 60–89 years)	
Chronic osteoarthritis and spondylitis	17
Chronic sacroiliac strain, sciatica	7
Chronic rheumatoid arthritis	3
Gout	2
Total	29

TABLE 2. *Dosage Schedules*

Dosage Schedule = four times daily	No. of Patients, Group A*	No. of Patients, Group B*
Meticorten 5 mg. & Trilafon 8 mg.	14	19
Meticorten (or Meticortelone) 5 mg. & Trilafon 4 mg.	19	32
Meticorten 2.5 mg. & Trilafon 4 mg.	0	17
Meticorten (or Meticortelone) 2.5 mg. & Trilafon 2 mg.	17	29

* These totals exceed the number of patients in the series [50], since several patients received more than one dosage.

patients so treated, but half of them were somewhat drowsy. The same dosage of Meticorten with half the dosage of Trilafon proved equally effective in 17 of 19 patients and there was a 50 per cent reduction in the incidence of drowsiness; the failures occurred in 1 case of traumatic hemarthrosis of the knee joint (later requiring multiple aspirations) and in 1 case of severe sacroiliac sprain. Meticorten (2.5 mg.) and Trilafon (2 mg.) four times daily provided relief in 16 of 17 patients, and had no soporific side-effect.

Group B (29 hospitalized elderly subjects). The high-dosage combinations of Meticorten or Meticortelone with Trilafon were as effective among the older age group as among the younger, but drowsiness was more frequent. These relatively large amounts of Trilafon were required in 4 extremely agitated senile patients with osteoarthritis. In general, however, the lower dosage of Trilafon in combination with the larger amounts of adrenal steroid was just as effective and less soporific. Meticorten or Meticortelone (2.5 mg.) and Trilafon (4 mg.) four times daily was almost as effective as the larger amounts, and appeared to be the optimal level among older persons. Of 29 patients who received this dosage, 25 were benefited substantially and there were no side-effects. The 4 failures included 2 cases of severe spondylitis, 1 of gout, and 1 of sciatica.

Side-effects

Somnolence, which occurred occasionally in our series, was the only side-effect. During the administration of 24 mg. or 32 mg. of Trilafon daily, 8 of 14 patients in group A and 14 of 19 patients in group B became drowsy. With 16 mg. of Trilafon daily, only 4 of 19 patients in group A and 5 of 18 patients in group B experienced this effect. No patient in either group who received 8 mg. of Trilafon daily was affected.

Retention of fluid, which has been reported following administration of cortisone or hydrocortisone, rarely occurs with Meticorten or Meticortelone. In none of our subjects was there retention of fluid, although a few elderly cardiac patients in group B who received the higher dosage of both drugs had increased peripheral edema in the legs. Halving the dosage of Trilafon but not of the steroid resulted in diminution of the edema, whereas when the dosage of steroid but not of Trilafon was lowered, the edema continued. Therefore, it is likely that relative inactivity provoked this effect; the patients became more or less immobilized in a favorite chair.

Representative case histories

Group A. A 46-year-old man sustained acute low-back trauma, with excruciating pain, while attempting to lift a box weighing 150 pounds. When seen twenty-four hours after injury, the patient was in great distress, was unable to turn, and exhibited marked kyphoscoliosis on walking. The diagnosis was strain of the sacroiliac ligaments. Trilafon (4 mg.) and Meticorten (5 mg.) were administered four times daily. Marked relief occurred within twenty-four hours; the patient was able to straighten his back and to sleep at night. Within seventy-two hours the pain had subsided completely and he was able to return to work. Dosage was lowered gradually to 2 mg. of Trilafon and 2.5 mg. of Meticorten three times daily, and the drugs were finally discontinued after one week. At the time of check-up two months later, there was no recurrence.

Group B. An 82-year-old woman presented chronic osteoarthritis with intermittent exacerbations of swelling and pain in the fingers and spine. There was a 26-year history of progressive hypertrophic arthritis with Heberden's nodes, distortion and atrophy of the fingers and toes, numerous osteophytes of the spine, and limitation of motion in the hands, feet and lumbodorsal spine. During an acute episode of swelling and pain in the joints of both hands, the patient received Trilafon (4 mg.) and Meticorten (5 mg.) three times daily. Marked relief occurred within three days; previous attacks usually had lasted two to three weeks. She became drowsy on the third day and dosage was halved. Symptoms remained under control. Dosage was further reduced gradually and therapy was discontinued after one month. Another acute episode developed five weeks later and the patient again received the reduced dosage, with rapid improvement. She is now being maintained on Trilafon (2 mg.) and Meticorten (2.5 mg.) once daily, and has remained free of attacks.

DISCUSSION

The degree of relief of pain and spasm is significantly greater when both Trilafon and steroids are used than when the steroids are used alone. Recovery occurs 30 to 40 per cent more rapidly if the emotional component is reduced by a suitable tranquilizing drug, and patients endure the period of disability with more equanimity.

Trilafon is extremely effective against tension and anxiety. In patients with agitation or other overt emotional symptoms, a dosage of 4 or 8 mg. three or

four times daily is desirable; in other patients, the 2-mg. tablet four times daily is generally adequate.

In the treatment of disorders of the joints, both prednisone and prednisolone reduce the pain, inflammation and swelling. Neither agent appears to provoke fluid retention, even among elderly cardiac patients. We prefer the 2.5-mg. to the 5-mg. tablet because of greater flexibility of dosage.

SUMMARY AND CONCLUSIONS

Traumatic and inflammatory arthralgias in 21 ambulatory middle-aged patients and 29 hospitalized elderly patients were treated with a tranquilizing drug (Trilafon) in addition to prednisone (Meticorten) or prednisolone (Meticortelone). Several strengths of each agent and various combinations were used in order to determine optimal dosage levels. The highest dosage of prednisone or prednisolone was 5 mg., and the lowest 2.5 mg., four times daily. The highest dosage of Trilafon was 8 mg., and the lowest 2 mg., four times daily.

Fear and anxiety, which are common in patients with disorders of the joints, exaggerate the primary disability. Therefore, addition of a tranquilizing agent to standard adrenal steroid therapy significantly accelerates recovery. Marked relief of pain and spasm occurred rapidly in nearly all patients in this series.

There were no side-effects attributable to the adrenal steroids used, and the only side-effect of Trilafon was drowsiness, seen in some patients who received relatively large doses.

The optimal dosage appears to be 2.5 mg. of prednisone or prednisolone and 2 mg. of Trilafon three or four times daily. Larger amounts may be used in resistant cases or for short-term therapy. Smaller amounts are often adequate for maintenance therapy in chronic cases after maximal improvement has been achieved.

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TREATMENT OF CARDIAC INFARCTION WITH ORAL ANTICOAGULANTS

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It is now widely accepted that the use of oral anticoagulant drugs in the few weeks following cardiac infarction significantly reduces the occurrence of thrombo-embolic complications and the mortality rate (1–3). The main purpose of this paper is to record the results of such treatment in a group of patients with cardiac infarction compared with a control series not treated with anticoagulant drugs studied over the same period of time. This represents an extension of a study previously made (4). In addition, it was thought worthwhile to carry out a follow-up study of both groups of patients in order to ascertain the recurrence rate of cardiac infarction and whether a four-week course of oral anticoagulants had any effect on the prognosis after the treatment was stopped. A study exactly on these lines apparently has not been made previously. Tudhope and Donald (5) reported that the proportion of patients dying during the latter eleven months of the first year (after the anticoagulant therapy was stopped) was considerably less in their series than in previously reported series in which anticoagulants had not been used. They did not, however, compare their series directly with a control group admitted to the same hospital and observed at the same time.

MATERIAL

The patients included in this survey had been admitted to the wards of Aberdeen Royal Infirmary and Woodend General Hospital during the period 1949–1956. The diagnosis of cardiac infarction was based on the history and physical examination. In the majority of cases the diagnosis was confirmed by electrocardiograms but, since the facility with which these could be obtained varied at different times throughout the survey, some cases without electrocardiographic confirmation were included because the history and physical findings were considered sufficiently characteristic to justify the diagnosis.

Patients were excluded from the survey if 1) the infarction had occurred more than forty-eight hours before admission to hospital, as treatment in the early stages is particularly important in improving the prognosis; 2) death had occurred within twenty-four hours after admission, as oral anticoagulant drugs do not have a significant effect within this time; and 3) the period of observation in hospital had been less than three weeks.

The patients were divided into 2 main groups, as follows:

Group I consisted of 162 patients who, in addition to the usual supportive measures, were treated with oral anticoagulant drugs in the form of ethyl biscoumacetate or phenindione. This form of therapy was continued for about four weeks.

Group II consisted of 311 patients who had received conventional therapy without anticoagulant drugs. These constitute the control series.

The average duration of hospital stay in both groups was forty days.

RESULTS

Mortality rates

Table 1 shows the results obtained in Group I during the period of anticoagulant therapy. Table 2 shows the results in the control series.

It is seen that, in each decade, the mortality rate of patients with cardiac infarction treated with oral anticoagulant drugs was much less than in the control series. The percentage of patients surviving a thrombo-embolic complication was also less, but this difference was not so marked. Comparison is difficult between the total figures for Groups I and II because Group II contained a much higher percentage of older patients.

In order to study further the results in the older age-groups, the patients aged 60 years and over were divided into 5-year sections. The results are shown in Tables 3 and 4.

Table 4 shows that the mortality rate in the control series for ages 60–74 years varied between 36.2 and 38.7 per cent; and that over the age of 75 years, the mortality rate rose to over 50 per cent. In the treated series (Table 3), the numbers were much smaller in each age-group; nevertheless they show a re-

TABLE 1. *Patients Treated with Oral Anticoagulant Drugs—Group I*

Age in Years	No Complications	Non-fatal Thrombo-embolic Complications	Deaths	Total
40–49	25 86.2%	3 10.3%	1 3.5%	29
50–59	44 71.0%	13 21.0%	5 8.0%	62
60–69	37 82.2%	4 8.9%	4 8.9%	45
70–79	13 65.0%	2 10.0%	5 25.0%	20
80–89	4 66.7%	0 0	2 33.3%	6
Total.....	123 75.9%	22 13.6%	17 10.5%	162

TABLE 2. *Control Series—Group II*

Age in Years	No Complications	Non-fatal Thrombo-embolic Complications	Deaths	Total
40–49	15 62.5%	4 16.7%	5 20.8%	24
50–59	27 56.3%	11 22.9%	10 20.8%	48
60–69	51 47.7%	16 14.9%	40 37.4%	107
70–79	43 40.9%	13 12.4%	49 46.7%	105
80–89	11 40.7%	1 3.7%	15 55.6%	27
Total.....	147 47.3%	45 14.5%	119 38.2%	311

TABLE 3. *Patients Treated with Oral Anticoagulant Drugs—Group I—Aged 60+ Years*

Age in Years	No Complications	Non-fatal Thrombo-embolic Complications	Deaths	Total
60–64	25 83.3%	3 10.0%	2 6.7%	30
65–69	12 80.0%	1 6.7%	2 13.3%	15
70–74	9 56.3%	2 12.5%	5 31.2%	16
75–79	4 100.0%	0 0	0 0	4
80	4 66.7%	0 0	2 33.3%	6
Total.....	54 76.1%	6 8.4%	11 15.5%	71

TABLE 4. *Control Series—Group II—Aged 60+ Years*

Age in Years	No Complications	Non-fatal Thrombo-embolic Complications	Deaths	Total
60–64	26 55.3%	4 8.5%	17 36.2%	47
65–69	25 41.7%	12 20.0%	23 38.3%	60
70–74	30 48.4%	8 12.9%	24 38.7%	62
75–79	13 30.2%	5 11.6%	25 58.2%	43
80+	11 40.7%	1 3.7%	15 55.6%	27
Total.....	105 43.9%	30 12.6%	104 43.5%	239

TABLE 5. *Incidence of Thrombo-Embolic Complications (T.E.C.)*

Age in Years	Treated Series			Control Series		
	Number of Patients	Number of T.E.C.	Fatal T.E.C.	Number of Patients	Number of T.E.C.	Fatal T.E.C.
40–49	29	4 13.8%	1 3.4%	24	7 29.2%	3 12.5%
50–59	62	16 25.8%	3 4.8%	48	19 39.6%	8 16.7%
60–64	30	5 16.7%	2 6.7%	47	15 31.9%	11 23.4%
65–69	15	3 20.0%	2 13.3%	60	26 43.3%	14 23.3%
70–74	16	4 25.0%	2 12.5%	62	25 40.3%	17 27.4%
75–79	4	0 0	0 0	43	22 51.2%	17 39.5%
80+	6	2 33.3%	2 33.3%	27	10 37.0%	9 33.3%
Total.....	162	34 21.0%	12 7.4%	311	124 .39.9%	79 25.4%

duction in the mortality rate. Again, the mortality rate increased with increasing age.

Thrombo-embolic complications

The main effect of anticoagulant therapy is presumably to reduce the incidence of thrombo-embolic complications, including recurrence or extension of the initial thrombosis. Table 5 shows the number of such complications and the number which were fatal for patients in each decade. It is readily seen that the number of thrombo-embolic complications occurring in the treated series was much less than in the control series, and furthermore, the number of deaths from such complications was even further reduced.

It is evident from Table 6, which shows the number of deaths from each cause, that thrombo-embolic complications were still the most frequent cause of death even in the treated series. This would indicate that, although oral anticoagulant drugs reduce considerably the incidence of thrombo-embolic complications and the mortality resulting from them, such treatment does not prevent the occurrence of these complications in a significant number of cases.

Early deaths

Patients who died within twenty-four hours of admission to hospital were excluded from this survey because oral anticoagulant drugs take at least this

TABLE 6. *Causes of Death*

Cause of Death	Treated Series		Control Series	
	Age 40–59	Age 60+	Age 40–59	Age 60+
Recurrence or extension of coronary thrombosis	3	8	8	47
Other thrombo-embolism	1	0	3	21
Cardiac failure	0	1	1	20
Peripheral circulatory failure	0	1	2	14
Rupture of heart	2	0	0	0
Adams-Stokes' attack	0	1	1	0
Bronchopneumonia	0	0	0	2
Total	6	11	15	104

length of time to become fully effective. During the period under survey, 60 patients died during the first twenty-four hours. None of these had been treated with heparin. The 2 main causes of these early deaths were extension or recurrence of the coronary thrombosis and peripheral circulatory failure. In an attempt to reduce this number, it is now our practice to give intravenous heparin on admission and to continue this treatment for at least twenty-four hours, by which time the oral anticoagulant drugs will have lengthened the plasma "one-stage prothrombin time" to a satisfactory level. Simultaneously, peripheral circulatory failure, if present, is treated with *l*-noradrenaline by intravenous infusion. At the present time, the number of cases so treated is unfortunately too small to allow comparison.

Follow-up

It was decided to complete this study with a follow-up of all the patients who had been discharged from hospital, in order to ascertain the number of recurrences and to compare the recurrence rate in the 2 series. Accordingly, questionnaires were sent to the doctors of all the patients who had sustained their infarction more than one year previously, asking for the following information:—

(a) Is the patient still alive?

(b) Have there been further episodes of cardiac infarction? If so, please give details.

(c) If patient is dead, please give date and cause.

In all, 292 questionnaires were sent out and 247 replies (84.6 per cent) were received. The condition of some patients remains unknown, because they left Aberdeen during the period of review and could not be traced. Other patients died of various diseases other than myocardial infarction, *e.g.*, cerebrovascular disease, cardiac failure, bronchopneumonia and carcinoma. These were all excluded from the survey.

Tables 7, 8 and 9 show the analysis of the findings for the 40–59 year age-group, the 60+ year age-group and for all ages, respectively. These were all further subdivided into the treated series and the control series according to the group to which the patient originally belonged. The condition one year, two

TABLE 7. *Follow-up of Patients Aged 40–59 Years*

	Treated Series			Control Series		
	At 1 yr.	At 2 yrs.	At 5 yrs.	At 1 yr.	At 2 yrs.	At 5 yrs.
Number of patients	54	46	13	43	38	15
Number of recurrences	8	9	5	5	5	5
Percentage of recurrences	14.8%	19.6%	38.5%	11.6%	13.2%	33.3%

TABLE 8. *Follow-up of Patients Aged 60+ Years*

	Treated Series			Control Series		
	At 1 yr.	At 2 yrs.	At 5 yrs	At 1 yr.	At 2 yrs.	At 5 yrs.
Number of patients	46	27	5	98	76	29
Number of recurrences	4	8	3	28	34	20
Percentage of recurrences	8.7%	29.6%	60.0%	28.6%	44.7%	69.0%

TABLE 9. *Follow-up of All Patients*

	Treated Series			Control Series		
	At 1 yr.	At 2 yrs.	At 5 yrs.	At 1 yr.	At 2 yrs.	At 5 yrs.
Number of patients	100	73	18	141	114	44
Number of recurrences	12	17	8	33	39	25
Percentage of recurrences	12.0%	23.3%	44.4%	23.4%	34.2%	56.8%

years and five years after cardiac infarction was ascertained, and the number of recurrences for each series was stated, with the recurrence rate expressed also as a percentage of the number of patients remaining at each interval.

From Table 7 it can be seen that in the 40–59 year age-group, the number of recurrences increased with time. Secondly the recurrence rate for the control series was slightly lower than for the treated series, which would indicate that in this age-group there is no beneficial effect of oral anticoagulant drugs after the therapy is discontinued. Table 8 shows that, in the 60+ year age-group, the recurrence rate was on the whole much higher, and again increased with time. The figures for the treated series, however, are better than those of the control series. Analysis showed that in this age-group, the difference in the recurrence rate between the treated series and the control series at one year was statistically significant. This difference was not so obvious at two years, and was absent at five years, but at these times the numbers were too small for comparison. It is possible that this significant difference at one year is the result of more rapid and more efficient recanalization of the thrombus in the treated series. In experimentally produced arterial thrombosis in rabbits, Wright and others (6) found that in anticoagulant-treated animals the average time taken for recanalization was three and a half weeks, whereas in the control animals the arteries remained occluded even after several months.

In Table 9, which shows the data for all ages, it is evident that there was a difference in the recurrence rate which was similar to but less marked than that for the 60+ age-group, and was simply a reflection of the latter. In the treated series, the recurrence rate in the first year was 12 per cent. This figure is exactly the same as that found by Tudhope and Donald (5) in their survey of 100 cases reviewed at the end of one year after an initial four-week course of oral anticoagulant drugs for cardiac infarction.

SUMMARY AND CONCLUSIONS

Oral anticoagulant therapy significantly reduced the mortality rate in a series of 162 cases of cardiac infarction.

The incidence of thrombo-embolic complications and the mortality from these causes was also reduced. In this series, however, these complications remained the chief cause of death.

Many deaths occur soon after cardiac infarction. In an attempt to reduce this number, it is suggested that intravenous heparin be used until the oral anticoagulant therapy becomes effective.

It would appear that patients more than 60 years of age retain some beneficial effect from a short course of anticoagulant drugs and this effect lasts for at least one year.

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PSYCHIATRIC EVALUATION OF GERIATRIC PATIENTS ON AN OUTPATIENT BASIS: PRELIMINARY STUDY

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The number of patients admitted to State hospitals with the diagnosis of chronic brain syndrome associated with senility or cerebral arteriosclerosis is steadily increasing and approaches the number of patients admitted with the diagnosis of schizophrenia (1). During the years 1955 and 1956 more than 33 per cent of all patients admitted to the Osawatomie State Hospital in Kansas were over 65 years of age, and more than 40 per cent were over the age of 60. A great number of these patients were retained after the 90-day observation period. At the present time about 45 per cent of all the patients at the hospital belong to the geriatric group.

According to Kolb (2), the number of persons over 65 in the United States increased 57.5 per cent from 1936 to 1957, and the number of first admissions of persons 65 and over to state mental hospitals increased 95.5 per cent. Using statistical materials, Bettag and his associates (3) predict that in the year 2000, 67 per cent of the patients in State hospitals and 13.2 per cent of the national population will be over 65.

Whereas in the past, a feeling of helplessness and lack of interest in this problem has been a characteristic feature of most psychiatrists, in recent years, due to the publications of Gitelson (4), Goldfarb (5), Meerloo (6), Busse *et al.* (7), Linden (8) and others, a better understanding of the emotional problems and needs of geriatric patients has taken the place of the apathetic, nihilistic "custodial care" attitude. Furthermore, thanks to the efforts of Cosin (Oxford, England) (9) and of Cameron (Montreal, Canada) (10), geriatric units have been created which emphasize Day-Center treatment and an active Rehabilitation Service, and attach great importance to social relationships of geriatric patients in regard to their readjustment in their own family and community.

An active treatment program in the hospital alone is not sufficient to help the situation. Placement of geriatric patients ready to leave the hospital is a complicated procedure. Very often the return to their families does not bring the desired results, because the stress situation (which caused the patient's hospitalization) remains unchanged. Moreover, placing them in foster homes or nursing homes, frequently does not solve this difficult problem.

Therefore, at Osawatomie State Hospital a method was tried, with the aim of keeping many geriatric patients from being admitted to the hospital after referral by Court order for a 90-day observation period. The applications for all patients aged 60 and older (with a few emergency exceptions) were carefully considered. Before any decision regarding hospitalization was made, each pa-

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tient was thoroughly examined physically, neurologically and psychiatrically in the Outpatient Clinic of the hospital by a trained psychiatrist.

It became evident that a great number of applications for admittance of geriatric patients to the State Hospital were vague and incorrect. Frequently, statements that the old person was disturbed, threatening and in urgent need of hospitalization could not be confirmed when he (or she) entered the hospital. It is well known that many geriatric patients who are noisy, restless and agitated at home, react quickly to the protective environment of the hospital and improve when the situation of stress and strain is taken from them. But, we had to ask ourselves: Was it not possible to eliminate this situation of stress by changing the environment outside the hospital instead of hospitalizing the patients? The results of the evaluation of these elderly patients before they were admitted to the hospital are, therefore, of great importance. The screening of the applications and the examinations on an Outpatient Basis started in September 1957 and have yielded some interesting findings.

RESULTS

Twenty-eight geriatric patients in the age group 65–85, referred for a 90-day observation period by Court order were examined physically, neurologically and psychiatrically (Table 1). During the five-month period ending January 10, 1958, only 7 of these 28 patients were admitted to Osawatomie State Hospital, 7 were sent to nursing homes, and 14 were returned to their families. The family physician of each patient not hospitalized received an extensive report about the evaluation, with further recommendations for treatment. Many patients were told to return to the hospital whenever further advice was needed, and the relatives were notified that they could feel free to visit our Outpatient Clinic in case the proposed treatment program outside the hospital did not show the expected results within a month.

A typical case history will help to illustrate our procedure:

P.R. (*OSH* 806) was a 75-year-old married male janitor. He was accompanied by his wife and daughter. His wife was 51 years of age, and they had been married eleven years. It was the second marriage for both. It was stated in the social history that the patient during the previous two years frequently became angry and fought with his wife. He had also wandered away from home and got lost. When found by the police, he could not understand why everyone was so excited and interested in his whereabouts. He had been treated by his family physician with tranquilizers.

The patient came to our hospital for 90-day observation, by Court order. At the interview he was friendly and cooperative and answered questions willingly. He was neatly and cleanly dressed and was apparently used to taking good care of his personal appearance. His intellectual faculties were poor, however. He was not oriented as to time and place and had a severe memory defect for recent and remote events. He believed himself to be 57 years of age and that his birthday was December 8, 1950; he did not remember what meals he had eaten the day before. Although he had a fifth-grade education, he did not know how to multiply 9 by 9 and could not name the capital of Missouri. In his life time he had never had a hobby of any kind, except participating in church activities. When asked about his wandering away, he answered that he "just had to go" and did not know why. He liked to walk through the country, but would always return. "I never want to go too far," he said.

TABLE 1. *Evaluation of Geriatric Patients on an Outpatient Basis*
(Osawatomie State Hospital, September 1, 1957 through January 10, 1958)

Patient	Age (yrs.)	Date of Evaluation	Diagnosis	Disposition of Case
1. B.C.	78	Sept. 6, 1957	Chronic brain syndrome associated with senile brain disease, chronic, severe, without psychotic reaction	Family care; application withdrawn
2. M.H.	68	Sept. 20, 1957	Hysterical personality with obsessive-compulsive features	Referred to nursing home
3. F.W.	78	Sept. 30, 1957	Chronic brain syndrome associated with senile brain disease with behavioral reaction	Family care; application withdrawn
4. E.S.	66	Oct. 2, 1957	Aphonia due to conversion hysteria	Family care
5. L.P.	73	Oct. 2, 1957	Chronic brain syndrome associated with cerebral arteriosclerosis with psychotic reaction, severe	*Admitted* to hospital as an emergency case
6. W.D.	80	Oct. 3, 1957	Chronic brain syndrome associated with senile brain disease with behavioral reaction	Referred to nursing home; application withdrawn
7. I.A.	77	Oct. 10, 1957	Chronic brain syndrome associated with senile brain disease with behavioral reaction, moderate	Family care
8. M.S.	66	Oct. 21, 1957	Without psychosis	Family care; application withdrawn
9. G.M.	73	Oct. 25, 1957	Psychotic depressive reaction	*Admitted* to hospital
10. E.H.	82	Oct. 28, 1957	Chronic brain syndrome associated with cerebral arteriosclerosis without psychotic reaction	Referred to nursing home; application withdrawn
11. C. R.	82	Oct. 30, 1957	Chronic brain syndrome associated with cerebral arteriosclerosis, severe, with behavioral reaction	Family care; deceased
12. P.R.	75	Nov. 4, 1957	Chronic brain syndrome associated with senility; behavioral reaction, mild	Family care
13. E. A.	78	Nov. 8, 1957	General paresis with psychotic episodes	*Admitted* to hospital
14. E.R.	69	Nov. 13, 1957	Adjustment reaction of late life with depressive features and signs of anxiety	Family care; receiving medication
15. I.H.	67	Nov. 20, 1957	Adjustment reaction of late life	Family care; application withdrawn
16. A.E.	76	Nov. 22, 1957	Manic depressive psychosis, manic type	*Admitted* to hospital
17. A.N.	83	Nov. 25, 1957	Without psychosis	Family care; application withdrawn

18. F.B.	73	Dec. 2, 1957	Chronic brain syndrome associated with senile brain disease, severe, with behavioral reaction	*Admitted* to hospital
19. M.A.	65	Dec. 4, 1957	Psychoneurosis; conversion reaction with some depressive features	Referred to nursing home
20. M.W.	85	Dec. 29, 1957	Chronic brain syndrome associated with cerebral arteriosclerosis without psychotic reaction, moderate	Under physician's care in her own home
21. A. L.	77	Dec. 9, 1957	Organic brain disease due to unknown causes, with psychotic reaction in remission	Under physician's care in her own home
22. G.S.	69	Dec. 18, 1957	Chronic brain syndrome associated with cerebral arteriosclerosis, with psychotic reaction	*Admitted* to hospital
23. J.B.	80	Dec. 27, 1957	Diagnosis deferred	*Admitted* to hospital
24. L.S.	70	Dec. 30, 1957	Psychoneurosis; anxiety reaction	Individual psychotherapy every 3 wks. on outpatient basis
25. C.P.	80	Jan. 6, 1958	Chronic brain syndrome associated with cerebral arteriosclerosis, severe, with behavioral reaction	Referred to nursing home
26. L.G.	72	Jan. 6, 1958	Senile brain disease associated with behavioral reaction	Referred to nursing home
27. C.H.	65	Jan. 8, 1958	Without mental disorder	Under physician's care in her own home
28. D.M.	79	Jan. 10, 1958	Chronic brain syndrome associated with senility, with behavioral reaction	Referred to nursing home

Addendum: The following 4 patients were withdrawn from the study, without coming in for examination: L.C. was scheduled for admission on December 9, 1957. Did not come. J.D. was scheduled for admission on December 4, 1957. Probate Judge called stating that the patient's condition had improved. C.M. had received medication, with resulting improvement. F.P. was scheduled for December 11, 1957. Probate Judge called saying patient had been treated with tranquilizers and had improved.

His thought processes were neither slow nor fast and his thought content was not delusional. Hallucinations were not detected. Two months before the interview he started working as a janitor every night and seemed to like his job. He quit his job seven weeks later because of his confusion and wandering away and getting lost. He did not have insight into his condition and did not reveal signs of anxiety. He denied worrying about money or anything else. When asked about his relationship with his wife, he answered: "I love my wife and I get along with her very fine."

Physical examination: Blood pressure was 180/90. A systolic murmur was heard over the base of the heart; it was not transmitted. The second aortic sound was accentuated and there were premature ventricular contractions. A cataract was present in the right eye and a cataract had been removed surgically from the left eye. Neurologic examination yielded normal results. There were no other significant physical findings.

After the interview with the patient, the wife and daughter, together with the social worker, were called into the office of the psychiatrist. The wife expressed disappointment in the marriage because she expected her husband to take care of her. This he had been able to do for the first few years until he grew older and less physically fit. She was considerably younger than he and desired more material things than he could provide. Bills for their new car and household items mounted until she had to go to work the previous year in order to meet the expenses. Her work kept her away from home during the day and his work kept him busy at night. These circumstances appeared to be the reason why the patient, who was left alone most of the day, became upset and wandered away from home. It was explained in the interview that this situation had to be changed. The wife should stay at home more often than formerly and should give her husband more loving care in order to eliminate his feeling of loneliness and rejection. Otherwise he might become really emotionally disturbed in the future. With these recommendations and the prescription of a tranquilizer for ten days, the patient was sent home.

It was found necessary to follow up the condition of each patient after the evaluation. The Social Service of the hospital asked the relatives to report on a regular monthly basis. Up to the present, none of the 28 patients appraised in the Outpatient Clinic and not admitted to the hospital, has returned for hospitalization. One of them is being treated by individual psychotherapy and comes to the hospital for one hour every third week.

The results have already indicated that this method of evaluation and treatment of geriatric patients not only permits a more optimistic outlook regarding their general psychiatric treatment, but establishes a sound principle for decreasing their hospital rate. These elderly people threaten to fill our mental institutions, whereas they could be treated on the outisde with better results. We are in complete agreement with Cosin's statement that "the increased number of admissions of old folk to chronic sick hospitals and mental hospitals, is due in part to a failure to provide facilities in a field of preventive medicine."

SUMMARY

In a five-month period, 28 geriatric patients were evaluated and treated on an outpatient basis at the Osawatomie State Hospital. All of these patients had been referred by Court order for a 90-day observation period. Only 7 patients were admitted to the hospital; 7 were sent to nursing homes, and the remaining 14 were returned to their families with our recommendations to the family and general practitioner for continued treatment outside the hospital. The reasons for such a procedure are discussed and a typical case history is presented.

As the geriatric wards in psychiatric hospitals become increasingly overcrowded, the careful evaluation of patients on an outpatient basis is an important way to meet this problem.

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ADJUNCTIVE MEDICATION (KOLANTYL BISCULES) IN GERIATRIC PATIENTS WITH GASTRO-INTESTINAL DISORDERS

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INTRODUCTION

Only in recent years has it become apparent that most disorders of the gastro-intestinal tract involve multiple etiologic or contributory factors. In these disorders, symptomatic treatment is indicated whenever definitive treatment must be delayed, is initially ineffective, or is unavailable. For example, disturbances of the psyche as well as of the autonomic nervous system, alterations in body chemistry, and dietary indiscretions all influence the course of peptic ulcer. Many attempts have been made to develop agents that will provide relief of distress brought about by any one of these factors. Countless drugs have been employed, alone and in combination, with varying degrees of success in the medical management of peptic ulcer.

One such combination of drugs, Kolantyl,[1] has been distinctly effective in the treatment of peptic ulcer and functional bowel disease. Its mode of action is fourfold: 1) a direct antispasmodic effect on the musculature of the gut and on the parasympathetic nervous system, due to the dicyclomine; 2) balanced antacid activity, due to aluminum hydroxide and magnesium hydroxide; 3) inactivation of lysozyme and pepsin by sodium lauryl sulfate; and 4) the demulcent effect of methylcellulose. Hufford (1) studied the effect of Kolantyl tablets on 30 patients with ulcerative and spastic disease of the gastro-intestinal tract. Because of the gratifying results, he recommended the use of this drug in conjunction with diet, sedation, psychotherapy and surgery when indicated. Johnston (2) employed Kolantyl in the treatment of 17 cases of peptic ulcer. The majority of his patients experienced symptomatic improvement after the first day, and all obtained complete relief within one week. Miller (3) reported that Kolantyl was well tolerated by his patients and was more effective in the treatment of duodenal ulcer and functional bowel disease than was dicyclomine[2] alone. He attributed the therapeutic superiority of Kolantyl to its ability to inactivate lysozyme.

It is well known that patients restricted to the current rigid, monotonous ulcer diets and medications eventually resent them, and in some instances discontinue taking them. This attitude becomes increasingly prevalent with advancing age. Unfortunately, gastro-intestinal disorders referable to hyperacidity occur as commonly in elderly as in young adults. Accordingly, geriatric patients as a

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[1] Kolantyl is the trademark of The Wm. S. Merrell Company, Cincinnati 15, Ohio for its combination of dicyclomine (5 mg.), sodium lauryl sulfate (25 mg.), methylcellulose (100 mg.), magnesium oxide (200 mg.), and aluminum hydroxide gel (400 mg.).

[2] Bentyl is a trademark of The Wm. S. Merrell Company for its brand of dicyclomine.

group present an important problem in the medical management of gastro-intestinal disorders.

The present study is an attempt to evaluate a new dosage form of Kolantyl (the Biscule[3]) in the adjunctive treatment of gastro-intestinal complaints resulting from, or associated with gastric hyperacidity. Symptomatic manifestations of this condition are epigastric distress, abdominal pain, chest pain, heart burn, gas, sour stomach, bowel irregularities, nausea, vomiting, regurgitation, and abdominal distention. In older patients who experience these symptoms, the degree of hyperacidity is often relative and may not be demonstrable by laboratory tests.

PATIENTS AND METHODS

Fifty-four patients,[4] ranging in age from 33 years to 79 years (average 54.6 years), were given the Kolantyl Biscules for a sufficient period of time to permit valid conclusions as to the effectiveness of treatment. There were 21 females and 33 males. The usual instructions to the patient were to take 1 or 2 Biscules every three hours, or as needed. The period of treatment in most cases ranged from six to twelve weeks, although in a few cases it was as long as eighteen months. The diet was usually restricted. Many patients received vitamins, and when necessary, sedatives, informal psychotherapy, and occasionally other general and specific measures. Those in whom the symptoms had been fairly well controlled by previous ulcer treatment received the Biscules as a substitute for antacid or antispasmodic agents; however, some patients continued to receive supplementary amounts of these drugs.

The chief disorders among the 54 patients were: peptic ulcer in 23 (18 duodenal and 5 gastric); functional gastric disturbances in 22; esophagitis, gastritis or duodenitis associated with hiatal hernia or peptic ulcer in 27; and gastro-intestinal irritation due to drug-induced hyperacidity in 4.

RESULTS

The 40 normal persons who tried the Biscules confirmed the findings in the larger number of patients that this new dosage form of Kolantyl was well tolerated. Symptomatic improvement was graded from − to +++ (ranging from lack of response to complete cessation of symptoms). Forty-two (77.7 per cent) of the 54 patients experienced +++ improvement; 7 (13.0 per cent) obtained moderate or ++ relief; 1 (1.9 per cent) had only slight or + relief; and 4 (7.4 per cent) failed to obtain any relief (Fig. 1). That there was a prolonged antacid effect, is shown by the duration of relief from symptoms. Elderly patients with gastro-intestinal complaints associated with relative hyperacidity between meals experienced satisfactory relief from 1 or 2 Biscules, taken one to two hours after each meal. In younger patients with duodenal ulcer, the Biscule was used as a supplement to regular Kolantyl medication for between-meal feedings and bedtime snacks. The combination in the Biscule of food substance to combat hunger and of antacid to neutralize excessive acidity (whether relative or absolute) makes it a better therapeutic agent than the usual between-meal "snack."

[3] Biscule is the trademark of The Wm. S. Merrell Company for its medicated wafer.

[4] More than 75 patients received the medication, but some were not included in the study because of inadequate follow-up. Forty normal persons were asked to ingest these Biscules, in order to determine acceptability to the patients.

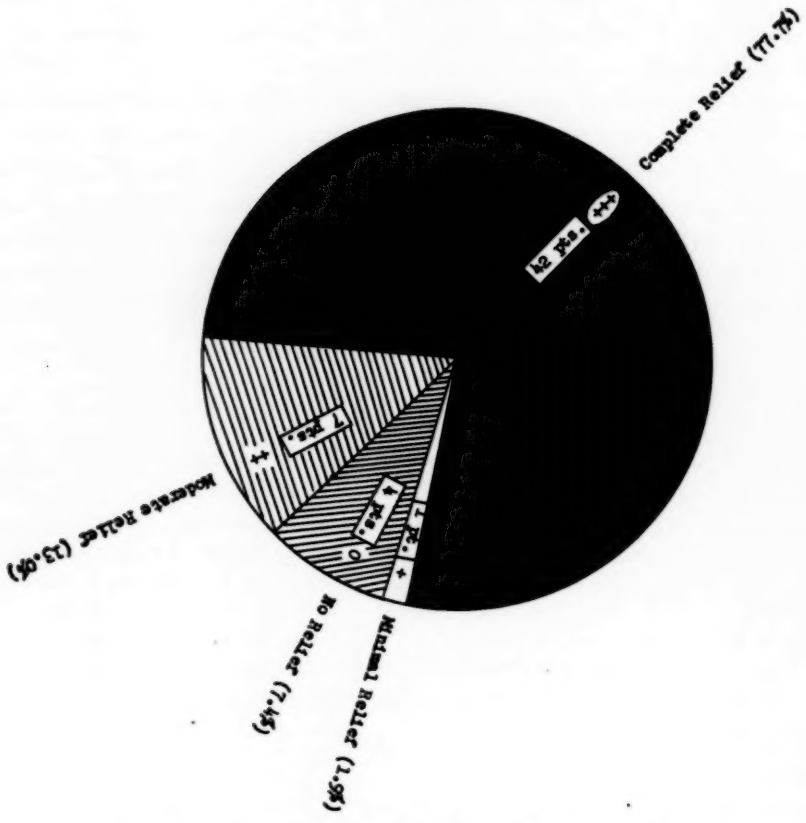

FIG. 1. Symptomatic response to Kolantyl Biscules.

In comparing their response to the Biscule with that previously obtained to Kolantyl gel, most patients thought that this new form of the drug was as effective as the gel therapeutically. The Biscule, however, was preferred because of: 1) the convenience of between-meal use, especially away from home and office; 2) the improved taste compared with the usual antacids; and 3) better control of symptoms than with supplementary feedings, as the wafer served both as a food substance and as an effective neutralizer[5]. Although the usual therapeutic response to Kolantyl gel is quite satisfactory, the clinical response to the Biscule form is even more so, because of the high degree of patient acceptability.

Only 2 of the 54 patients complained of undesirable features of the Biscule. One woman objected to the taste. Another had a recurrence of allergy to milk; after the first few doses of the medication she experienced nasal allergic manifestations such as sneezing, congestion and coryza, so the drug was discontinued.

[5] According to the standard U.S.P. antacid determination procedure as employed for aluminum hydroxide, 1 Kolantyl Biscule neutralizes 175 cc. of 0.1 *N* HCl. The normal stomach usually contains the equivalent of 60-80 cc. of liquid which has the acid value of 0.1 *N* HCl. One Biscule is equivalent in antacid neutralizing power to 1 Kolantyl tablet. The Kolantyl Biscule has proved to be stable and to maintain its neutralizing power, regardless of age.

No undesirable anticholinergic actions of the drug were observed, as shown by the lack of effect on salivary secretions, visual accommodation, and bladder or rectal tone.

CONCLUSIONS

The therapeutic effectiveness of Kolantyl is unaltered by incorporation into the new Biscule form. There are certain obvious advantages to the use of the Biscule. Among these are the added calories (approximately 45 calories per unit) and protein (0.45 Gm. per unit) provided by the biscuit base. Moreover, the bulk furnished by the wafer aids in counteracting and absorbing free acid in the stomach.

Probably the greatest advantage of the Kolantyl Biscule lies in the high degree of patient acceptability. This form of medication is convenient to take and provides the patient with a pleasant change from the usual, potentially monotonous, medical regimen. Since the Biscule is a combination of highly effective agents incorporated into a palatable wafer form, it is especially suitable for older patients who find no great appeal in therapeutic agents which resemble medicine.

Kolantyl Biscule therapy is notably free from side-effects, and represents a valuable addition to the medical management of organic or functional gastrointestinal disorders referable to hyperacidity. The medication should be used in conjunction with specific and supportive measures when these are available or indicated.

SUMMARY

Fifty-four patients with complaints referable to gastric hyperacidity were treated with an antispasmodic-antacid compound (Kolantyl) in a new wafer form—the Biscule. The average age of these patients was 54.6 years. They were given the usual dose of 1 or 2 wafers three times daily for six to twelve weeks. Fifty (92.6 per cent) of the 54 patients reported symptomatic improvement; relief was complete in 77.7 per cent. Only 4 patients (7.4 per cent) failed to benefit from treatment. Very few of the patients (and none of 40 normal persons who tried the Biscules) failed to react favorably to the taste, appearance and texture. This new form of the drug was found to be virtually free from side-effects.

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HYPERTENSION IN ELDERLY PATIENTS: TREATMENT WITH A FIXED COMBINATION OF ANTIHYPERTENSIVE DRUGS

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Because antihypertensive therapy may produce severe side-effects, its use in geriatric patients entails special considerations. For example, elderly patients are known to suffer from acute delirium after taking bromides or barbiturates (1). Aminophylline, theobromine and theophylline are of doubtful antihypertensive value because their action is limited, and thiocyanate, because it increases capillary fragility, is contraindicated in patients over 60 (2). Ganglionic blocking agents are better suited for hypertensive emergencies than for prolonged therapy, as serious or fatal cerebrovascular accidents may occur upon withdrawal of these potent, short-acting hypotensive drugs (3). Moreover, geriatric patients appear to be particularly prone to such side-effects as constipation and urinary retention, both of which are associated with prolonged administration of even small dosages of ganglionic blocking agents.

It has been postulated that a more pronounced antihypertensive effect might be achieved by combining 2 or more antihypertensive agents, and that such a combination might result in a significant reduction in undesirable side-effects (4). Several investigators (5–7), using a fixed combination of rauwolfia, protoveratrine and phenoxybenzamine in non-geriatric patients, reported an increased antihypertensive effect and diminished side-effects. These results seemed promising enough to warrant a trial of this combination of drugs in geriatric patients.

MATERIAL AND METHODS

Forty-four geriatric female patients, all residents of a home for non-indigent elderly men and women, were selected for this study. They ranged in age from 67 to 99 years (average, 77 years) and had systolic and/or diastolic blood pressures above normotensive levels, as established by repeated sphygmomanometric measurements made with the patients in a sitting position. The normotensive level was taken to be 150/90 mm. Hg, as adapted from Master (8) and Monroe (9).

In addition to elevated blood pressure, the patients had symptoms such as marked dyspnea, edema and angina (either singly or in combination) and complained in varying degree, of fatigue, nervousness, dizziness, palpitation or headaches. Symptoms of arteriosclerosis, cardiac decompensation, senility and other diseases accompanied the hypertensive manifestations in 37 patients.

Although most of the patients had received antihypertensive therapy in the past, it was not possible, except in 8 cases, to determine what drugs had been used. In these 8 cases, rauwolfia, aminophylline or phenobarbital had been administered. The results of previous therapy, regardless of its nature, were unimpressive in the main, as indicated by the status of the patients with regard to blood pressure and clinical symptoms at the beginning of this evaluation.

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To permit the blood pressure to become stabilized, and to eliminate any effects that may have been carried over from previous therapy, placebo medication was given to 36 of the 44 patients for one month. The placebo capsules were identical in appearance to those that contained the active medication.

Following the placebo period, all the patients were treated with the active medication. Each capsule contained 12.5 mg. of rauwolfia, 0.1 mg. of protoveratrine, and 2.5 mg. of phenoxybenzamine[1]. Patients were given 1 capsule three times a day, usually before meals. This dosage schedule was adequate for all but 7 patients. The dosage for these 7 had to be increased to 4 capsules a day in order to obtain adequate control of blood pressure and other hypertensive symptoms.

Blood pressure measurements were taken with patients in a sitting position. Determinations were made weekly, except for occasional, brief interruptions. Changes in symptoms and reports of side-effects were also recorded each time. The evaluation lasted twenty-seven weeks.

RESULTS

Results were analyzed by 1) comparing the effects of placebo and active medications on blood pressure in 36 patients, 2) comparing blood pressures before, and at the end of active medication in all 44 patients, 3) comparing the incidence and severity of hypertensive symptoms, other than blood pressure, before and during therapy, and 4) noting the incidence and severity of side-effects accompanying the active medication.

Placebo versus antihypertensive drugs; effect on blood pressure

As one might expect, a variable effect on blood pressure was observed when a placebo was administered. As shown in Table 1, 10 of the 36 patients (28 per cent) experienced a reduction in systolic pressure that averaged 22 mm. Hg, and a reduction in diastolic pressure that averaged 13 mm. Hg. This decrease was in approximate agreement with that which has been observed in similarly placebo-treated hypertensive subjects (10). On the other hand, 16 patients (42 per cent) experienced rises in systolic and diastolic blood pressures that averaged 31 mm. and 17 mm. Hg, respectively. In 7 patients (19 per cent) there was a mixed response (either a rise or a fall in systolic pressure), and in 3 (11 per cent) there was no significant change. During placebo therapy, therefore, the average increase in blood pressure was greater than the average decrease. At the end of placebo therapy, none of the patients had a systolic or diastolic blood pressure within normotensive limits.

A more consistent effect on blood pressure was observed after the 36 patients had received treatment with the combination of rauwolfia, protoveratrine and phenoxybenzamine (Mio-Pressin). During this phase of the evaluation, 29 patients (80 per cent) experienced a reduction in systolic pressure that averaged 39 mm. Hg, and a reduction in diastolic pressure that averaged 18 mm. Hg. These reductions were exclusive of any that might have been obtained during the placebo period. In 5 patients (14 per cent) there was a mixed response, and in only 2 (6 per cent) was there an increase in blood pressure—average, 20 mm. Hg systolic, and 7 mm. diastolic.

[1] Mio-Pressin, trademark of Smith, Kline & French Laboratories, Philadelphia, Pa.

Comparison of blood pressures before, and at the end of drug therapy

Based on blood pressure levels and accompanying symptom-complexes before drug therapy in the 44 cases (post-placebo in 36), the patients were arbitrarily divided into Group A and Group B. Patients in Group A had extremely high systolic blood pressures (average, 208 mm. Hg) and moderately elevated diastolic pressures (average, 104 mm. Hg). Patients in Group B had high systolic pressures (average, 190 mm. Hg) but fluctuating normotensive diastolic pressures (average, 84 mm. Hg). The symptoms in Group B, however, were as marked as those in Group A.

The results in all 44 patients are shown in Table 2. The "pre-therapy" blood pressure measurements in 36 cases were those made following the use of placebos, and not those observed when drug medication was initiated. In Group A, the average reduction in blood pressure was 49/24 mm. Hg, whereas in Group B it was 30/4 mm. Hg.

The average duration of therapy was fifteen weeks for Group A, and thirteen weeks for Group B. In both categories, the average length of time required to achieve stable blood pressure levels was approximately seven weeks.

TABLE 1. *Comparison of Placebo and Rauwolfia-Protoveratrine-Phenoxybenzamine Combination in 36 Geriatric Hypertensive Patients*

Change in Blood Pressure	Placebo Therapy		Combination R-P-P Therapy	
	No. of patients	Avge. change in blood pressure (mm. Hg)	No. of patients	Avge. change in blood pressure (mm. Hg) from post-placebo level
Reduction—systolic/diastolic	10	22/13	29	39/18
Elevation—systolic/diastolic	16	31/17	2	20/7
Mixed response	7	−3/+5*	5	−27/−3*
No change	3	0	0	0
Total	36		36	

* Changes in blood pressure were added algebraically and averaged. Minus (−) sign = drop in blood pressure; plus (+) sign = increase in blood pressure.

TABLE 2. *Comparison of Effectiveness of Rauwolfia-Protoveratrine-Phenoxybenzamine Combination in 2 Groups of Geriatric Hypertensive Patients**

	Group A (20 patients)		Group B (24 patients)	
	Pre-therapy	R-P-P therapy	Pre-therapy	R-P-P therapy
Average systolic blood pressure (mm. Hg)	208	159	190	160
Average diastolic blood pressure (mm. Hg)	104	80	84	80
Average reduction in blood pressure (mm. Hg)		49/24		30/4
Time req'd for stabilization of s/d levels		7 wks.		7 wks.
Average duration of therapy		15 wks.		13 wks.

* For 36 patients the pre-therapy blood pressure levels were those obtained after the period of placebo administration.

Other hypertensive symptoms before and after drug therapy

Since mild or moderate dyspnea, edema and angina can be expected to respond favorably to antihypertensive medication, either directly or as a result of the reduced blood pressure, these symptoms were included in this evaluation only when they were prominent. Marked dyspnea, present in 5 patients at the start of therapy, was completely relieved in 1 and substantially relieved in 4. Marked edema, also present in 5 patients, was completely relieved in 3, but unchanged in 2. Edema and dyspnea, present in 6 patients, were completely relieved in 1, partially relieved in 3, and only slightly relieved in 2. Dyspnea, edema and angina, present in 2 patients, were only slightly relieved.

Dizziness, headaches or "heart-awareness" were reported by 22 of the patients at the start of therapy; only 9 patients reported these symptoms at the conclusion of the therapy.

Side-effects

Side-effects such as tiredness, fatigue or abdominal distress were reported by 18 patients shortly after the start of combination drug therapy. In 12 of them these mildly distressing effects disappeared within a week or two, without any change in regimen or supportive medication. The only remaining side-effects—and all were mild or moderate—were abdominal distress (2 patients), tiredness or fatigue (4 patients), dizziness (1 patient), and nervousness (1 patient).

General

Using the blood pressure response, the disappearance of other symptoms, and the presence or absence of side-effects as a basis for judging results, the effects of antihypertensive medication were good in 37 patients and poor in 7.

DISCUSSION

The most striking result of the use of this antihypertensive preparation was the large proportion (77 per cent) of patients in whom systolic and diastolic blood pressures were significantly reduced without the appearance of significant side-effects. Particularly encouraging was the absence of complaints of nausea and vomiting, constipation or nasal stuffiness, which in many instances may be severe enough to preclude the continued use of antihypertensive medication. Had any of these side-effects occurred, it is doubtful whether they could have escaped attention, since the patients were told to report any discomfort or distress.

Any drug or combination of drugs used in geriatric practice must be evaluated not only with respect to its ability to relieve symptoms of disease, but also in terms of its relationship to overall objectives in the management of old age. The aim of such management, particularly in modern institutions for the aged, is to make the last years of life as interesting and as active as physical and mental conditions permit. Drugs that alleviate one set of symptoms only to create a new set of discomforts (such as drowsiness, lethargy, confusion or nervousness) make the life of the elderly patient less interesting and less active. Because the hypotensive preparation used in this evaluation apparently did not alter the

everyday routine of these patients, it appears to be a more effective and safer form of therapy than has been previously available for the treatment of hypertension in the aged.

SUMMARY

A fixed combination of rauwolfia, protoveratrine and phenoxybenzamine (Mio-Pressin) was found to be an effective antihypertensive agent in 37 of 44 geriatric female patients. Over periods of thirteen to fifteen weeks, systolic and diastolic blood pressures were reduced slowly. The average weekly drop in systolic pressure was 5 points, and in diastolic pressure 2 points, before stable levels were reached within approximately seven weeks.

Side-effects were mild and infrequent. Two patients complained of abdominal distress, and 4 complained of tiredness or fatigue. One patient reported occasional dizziness, and another reported nervousness. None of the side-effects was severe enough to require withdrawal of the medication.

The rauwolfia-protoveratrine-phenoxybenzamine combination used in this study appears to be a safe and effective preparation for the treatment of hypertension in the aged.

Acknowledgment

Acknowledgment is given to the Directress, Sr. M. Celeste, and the nurses of the Stella Maris Hospice, Timonium, Maryland, for their valuable technical assistance.

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Abstracts of Current Literature

THE VALUE OF CHLOROQUINE IN RHEUMATOID DISEASE. A FOUR-YEAR STUDY OF CONTINUOUS THERAPY.

Bagnall, A. *Canad. M. A. J.* **77:** 182 (Aug. 1) 1957.

One-hundred and twenty-five patients with rheumatoid disease received chloroquine in a dose of 250 mg. daily—4 for less than six months because of toxicity, three-fourths of them for more than one year, half for more than two years, and one-fifth for more than three years. The series included, besides patients with rheumatoid arthritis, 17 with Marie-Strümpell spondylitis, 8 with arthritis of juvenile onset, and 10 with rheumatoid arthritis and psoriasis. There were both severe long-standing and recent cases of rheumatoid arthritis. Approximately half of the patients had received other intensive treatment for four months to six years previously, whereas the remaining half had been treated by other therapy for less than five months. With chloroquine, no subjective response is likely to become apparent in less than two weeks. An objective response is unlikely to appear before six to twelve weeks, and the maximum response may be delayed for six to twelve months. Therefore, additional therapy was given by means of adequate rest, exercise, salicylates, mild sedation and adrenocortical steroids, the latter being used in the initial stages of chloroquine medication. The criteria of the American Rheumatism Association for judging the stage of the disease and the degree of improvement in functional capacity were used. In 71 per cent of the patients with rheumatoid arthritis there was a complete remission or a major degree of improvement. A minor degree of improvement occurred in 11 per cent, and none in 17 per cent. Similar percentages of the 17 patients with Marie-Strümpell spondylitis were improved. Each disease state responded equally well. Improvement in work performance, hemoglobin levels, and sedimentation rates occurred as part of the benefit. Among those who failed to improve, many had prolonged severe rheumatoid arthritis. Toxic reactions which necessitated a reduction in the dosage of chloroquine or its discontinuation accounted for slightly more than half of the failures. Relapses occurred in 18 patients during treatment with chloroquine— in 4 during the second six months of therapy and in 14 during the second or third year of therapy. The dosage had been lowered in 13 patients because of toxicity. In 16 patients the relapse subsided within one to four months, with the same or with an increased dosage. It persisted in 2 patients, but was mild so that it constituted only a change from a Grade I to a Grade II response. Ninety per cent of the patients experiencing a remission or major improvement continued to take chloroquine. A total of 105 side-actions to chloroquine occurred in 70 of the patients. Three-fourths of the patients showing a reaction subsequently were able to take full dosage of the drug, but 10 per cent were forced to discontinue it. Dermatitis occurred in 35 per cent of the patients, and seasickness in 32 per cent. The less frequent side-actions included metrorrhagia, leukopenia, lymphedema, aggravation of psoriasis, and serum sickness. In a long-term, double-blind study involving 21 additional patients with rheumatoid diseases, the effects of chloroquine could be distinguished readily from those of placebo. The possible mechanism of action of chloroquine in rheumatoid disease is discussed. This drug appears to be highly satisfactory for the long-term control of rheumatoid disease.

GENERAL PRINCIPLES OF FRACTURE MANAGEMENT IN THE AGED.

Bick, E. M. *Surg., Gynec. & Obst.* **106:** 343 (March) 1958.

The distribution of fractures and dislocations in patients over the age of 60 years is much the same as in any adult group, with 3 exceptions. Fractures of the hip, the vertebra and the shoulder were found to represent 58 per cent of the total in a group of 516 persons

more than 60 years old. Fractures occur more frequently in females than in males; the ratio between the ages of 60 and 75 years is 3:1, but above 75 years it is 11:1. Bone repair in elderly persons appears to take place within the same span of time as in adults of all ages. The quality of bone produced will be conditioned by the quality of the bone before the fracture. No special technics apply to the treatment of fractures in the aged, but the objectives to be attained are limited by the lessened strength and resiliency of the musculoskeletal tissues. This means that 1) there is a greater need for a resting period between emergency care and definitive treatment; 2) the softness and compressibility of the bones render pinning and the use of screws and plates less dependable in the aged; forcible manipulation may destroy fracture surfaces to a degree that will be more deforming than if a less perfect, though adequate, reduction were accepted; 3) the decreased elasticity of the muscular and periarticular connective tissues lengthens the period of after-care and demands the gradual resumption only of ordinary activities rather than the performance of formal exercises as might be used in younger persons. Particularly is this true in the case of fractures of the shoulder and vertebrae. No specific effect of androgens or estrogens upon the rate of quality of bone repair has yet been observed. Getting the patient out of bed must not be undertaken until it can mean greater freedom of action for the patient. The simplest procedures compatible with a functional recovery adequate for his physical abilities will best serve the aged patient with a fracture.

16-α-METHYL CORTICOSTEROIDS. A NEW SERIES OF ANTI-INFLAMMATORY COMPOUNDS; CLINICAL APPRAISAL OF THEIR ANTIRHEUMATIC POTENCIES.

Boland, E. W. *California Med.* **88:** 417 (June) 1958.

Four new compounds which are 16-α-methyl analogs of hydrocortisone have been produced and their use in human subjects is being studied. They are 16-α-methyl 9-α-fluoroprednisolone (MK-125, hexadecadrol), 16-α-methyl 9-α-fluorohydrocortisone (MK-126), 16-α-methylprednisolone (MK-110), and 16-α-methylhydrocortisone (MK-117). Preliminary assays of the potencies of these compounds in laboratory animals indicated that they possessed, in comparison with hydrocortisone, enhanced anti-inflammatory activity and enhanced glycogenic activity (190 and 17 times, respectively). None of the compounds in the doses used caused sodium retention in adrenalectomized rats. The antirheumatic potencies of the new steroids were compared with that of prednisolone by changing the treatment from one drug to another and determining the number of milligrams required to maintain equivalent clinical improvement. Improvement was judged by lessening of subjective complaints, by measurement of changes in joint swelling and range of motion, by judging local tenderness and pain on motion, and by observing changes in the erythrocyte sedimentation rate. On this basis, the potency of 16-α-methyl 9-α-fluoroprednisolone was seven times greater, that of 16-α-methyl 9-α-fluorohydrocortisone three times greater, that of 16-α-methyl prednisolone approximately one-third greater, and that of 16-α-methyl hydrocortisone approximately 70 per cent as great as that of prednisolone. These comparisons were made in 21, 11, 7, and 12 patients, respectively. The average doses of the substances used were 1.57, 4.0, 7.43, and 13.0 mg., respectively. At these dose levels, none of the compounds induced signs of salt and water retention. It is pointed out that increased anti-inflammatory potency does not imply therapeutic superiority. Extensive clinical observations will be required to establish the therapeutic applicability of these compounds. 16-α-Methyl 9-α-fluoroprednisolone (hexadecadrol) administered for as long as four months has maintained satisfactory control of the rheumatoid arthritis in 86 patients in dosages of 0.6 to 2.8 mg. per day, the average being 1.6 mg. daily. To date, dosages as high as 4 mg. per day have not caused edema and there have been no significant gastro-intestinal side-effects. 16-α-Methyl-hydrocortisone appears to be worthy of thorough clinical evaluation. It has not produced edema in dosages up to 40 mg. per day.

ATEROGENESI UMORALE ED ETÀ (CONSIDERAZIONI SULL'ATTIVITÀ ATEROGENA IN 38 CASI DI ACUTE SOFFERENZA VASCOLARE) (HUMORAL ATHEROGENESIS AND AGE. OBSERVATIONS ON ATHEROGENIC ACTIVITY IN 38 CASES OF ACUTE VASCULAR INSUFFICIENCY).

Bonomo, I., and Minerva, V. *Gior. di Gerontol.* **5:** 811 (Aug.) 1957. (English abstract)

The distribution of blood lipids (Kunkel lipids test, determination of total cholesterol and cholesterol esters, alpha/beta lipoprotein ratio, total lipids) was studied in 38 patients with acute vascular symptoms (ictus, paresis, coronary artery disease, emboli) divided into 2 groups according to age. In middle-aged persons, a higher positivity of data for serum values was found as well as a close relationship with clinical symptoms. In older subjects, the blood values appeared to be altered less. Arcus senilis appeared to be closely related to an atherogenic blood pattern in the younger patients, but this relationship was less clear in the older ones. An active humoral stage in atherosclerotic disease was established and linked with middle age (40 to 60 years). At this time, pathologic lesions are related to changes in serum values, and the clinical symptoms depend upon the sites of lesions. In later years, changes generally labelled "sclerotic" may dominate the pathogenesis of atherosclerotic lesions.

SCHULTZ-DALE TEST FOR DETECTION OF SPECIFIC ANTIGEN IN SERA OF PATIENTS WITH CARCINOMA.

Burrows, D. *Brit. M. J.* **1:** 368 (Feb. 15) 1958.

A serologic test for carcinoma described in 1955 by Makari and Huck was investigated and its reproducibility verified. The test proved 96.7 per cent accurate among 301 patients with carcinoma and among 207 patients without carcinoma whose sera were tested. Possible reasons for the false negative and false positive results are discussed. It was not possible with the test to produce a positive result with the sera of 12 patients with sarcoma and 5 with leukemia—a finding without explanation. The test furnished no quantitative measurement of the amount of carcinoma present. It proved accurate in diagnosing tumors as small as one-half inch in diameter. Below that size, the accuracy decreased, so that the test would have no value in detecting small areas of malignant change as in a polyp or leukoplakia. A negative result postoperatively was found not necessarily to indicate a good prognosis. It often happened that a negative result did not become established until several weeks following an operation.

ABNORMAL RESPONSES TO MUSCLE RELAXANTS IN CARCINOMATOUS NEUROPATHY.

Croft, P. B. *Brit. M. J.* **1:** 181 (Jan. 25) 1958.

Three cases of carcinomatous neuropathy in the absence of a history of symptoms suggestive of myasthenia and 2 cases of carcinoma with an associated mild neurologic disorder are reported, in which prolonged states of neuromuscular block developed following the use of muscle relaxants. The presence of a neurologic disorder was not suspected in the latter condition until the abnormal response to a muscle relaxant occurred. The causes of abnormal response to muscle relaxants have been reviewed previously and include 1) central action of the blocking agent, 2) the narcotic action of other drugs used during anesthesia, 3) carbon dioxide retention as a result of hypoventilation, 4) electrolyte disturbance, particularly that of potassium, 5) cholinesterase deficiency, and 6) the combination of 2 types of blocking agent. The practical points that the reported cases illustrate are: 1) All patients with carcinoma who are likely to receive muscle-relaxing agents should be examined carefully in order to exclude the presence of a neurologic disorder, and the use of these agents avoided when there is any suspicion that a patient with carcinoma has a

neuromuscular disorder. Evaluation of the patient's sensitivity with a test dose of the drug to be administered is recommended. 2) Surgeons and anesthetists should be aware of the risks involved in administering muscle relaxants to patients in whom a carcinomatous neuropathy is suspected. The danger appears to be especially great in neuropathies due to bronchial carcinoma, so that bronchoscopy should be performed under local anesthesia alone. The need for a careful search for the carcinomatous growth in cases of carcinomatous neuropathy is emphasized. It is recommended that patients with different types of carcinomatous neuropathy be investigated intensively using clinical, biochemical, histochemical and electromyographic methods of study. These studies should be repeated at intervals because of the differences in time of onset of carcinoma and neuropathy, and particular attention should be paid to changes following the removal of a carcinoma.

ULTERIORI RISULTATI DI NUOVE TERAPIE NELLE SINDROMI PARKINSONIANE; ATTIVITÀ TERAPEUTICHE DEL 3-FENIL-3-β-DIETILAMINO-ETIL-2-6-DIOSSI-PIPERIDIN-CLORIDRATO SOMMINISTRATO ISOLATAMENTE E IN ASSOCIAZIONE CON RESERPINA E RITALIN (FURTHER RESULTS OF NEW THERAPY FOR PARKINSON'S DISEASE. THERAPEUTIC ACTIVITY OF 3-PHENYL-3-β-DIETHYLAMINO-ETHYL-2-6-DIOXY-PIPERIDINE HYDROCHLORIDE ADMINISTERED ALONE AND IN ASSOCIATION WITH RESERPINE AND RITALIN).

Giberti, F.; Gianniotti, G., and Spizzirri, S. *Gazz. med. ital.* **116:** 404, 1957; through *Ciba Literature Review* **3:** 70, 1958.

The results obtained with Aturbane orally in the treatment of 64 adults are reported. Almost all of the patients had either Parkinson's disease or postencephalitic parkinsonism. The optimum daily dosage, which varied greatly from one patient to another, averaged 15 to 17 mg. and was given in three to six fractional doses. The maximum daily dosage administered was 30 mg. Treatment usually lasted two months—longer in some cases. In the patients who showed a positive reaction, improvement generally commenced in a few days. Thirty-eight of the patients, most of whom were ambulatory, received Aturbane alone. A beneficial response was elicited in 63 per cent. Combination of Aturbane with Serpasil and Ritalin did not prove advisable. The results were assessed on the basis of both subjective and objective criteria. Hypertonia and tremor responded best, the facies becoming more expressive and the gait less stiff. The autonomic nervous manifestations were also beneficially affected, in that salivation, seborrhea and hyperhidrosis regressed. Psychic improvement was reflected in the decrease or disappearance of restlessness and hyperexcitability, as well as in enhancement of mood. Aturbane also proved effective in 3 cases of spastic torticollis. The drug was well tolerated—a finding confirmed by the results of various laboratory tests.

C-REACTIVE PROTEIN IN CANCER: A STUDY OF 216 PATIENTS.

Graf, L., and Rapport, M. M. *Cancer* **11:** 255 (Mar.–Apr.) 1958.

Serum C-reactive protein levels were determined in 216 patients with histologically proved carcinoma, using a recently developed quantitative complement-fixation method. The sera of one-third of the patients contained quantities of C-reactive protein too low for reliable determination. In another third, the concentrations were in the lowest tenth of the response range. Negative results and low values were found even in patients with metastatic disease. Therefore, the presence of C-reactive protein cannot serve as an indcator of the presence of carcinoma.

THE RATIONALE OF SUBTOTAL AND TOTAL COLECTOMY IN THE TREATMENT OF CANCER AND MULTIPLE POLYPS OF THE COLON.

Grinnell, R. S. *Surg. Gynec. & Obst.* **106:** 288 (March) 1958.

The long-term follow-up results in patients with multiple polyps and carcinomas of the colon treated by conservative measures were reviewed in order to determine how frequently

subsequent cancers of the colon occurred that might have been prevented by performing total or partial colectomy initially. Among 67 patients with multiple polyps of the colon, only 1 would have benefited by the more radical procedure. Among 66 patients with multiple cancers in whom partial or total colectomy might have been indicated, only 8 could have benefited from the more extensive operation. These represent a possible salvage of only 0.73 per cent of the whole group, which represents about one-sixth of the possible operative mortality alone. It is concluded that partial or total colectomy is not justified except in a few selected cases of multiple polyps or cancer of the colon.

SULL' IMPIEGO DI UN NUOVO CORTICOSTEROIDE NELLA TERAPIA DELLE ARTERIOPATIE CRONICHE PERIFERICHE (THE USE OF A NEW CORTICOSTEROID IN THE THERAPY OF CHRONIC PERIPHERAL VASCULAR DISEASE).

Guagliano, G., and Stoppani, L. *Gazz. internaz. med.* **62:** 179, 1957; through *Ciba Literature Review* **3:** 79, 1958.

Inflammation presumably plays a decisive role in the pathogenesis of obliterative arteriopathies. The authors, therefore, gave the intra-arterial administration of corticosteroids a trial in 12 patients, making repeated and accurate studies of the circulatory condition with the aid of fluorescein, oscillography, measurement of skin temperature, photoplethysmography, and arteriography. Each morning they injected 10 mg. of Ultracortenol (prednisolone trimethylacetate) into the femoral or radial artery, depending upon which extremity was affected. The venous return was blocked during the injection for a total of approximately twenty minutes. If the lesions were bilateral, Ultracortenol was injected bilaterally at the same time. The duration of treatment was twelve to fifteen days. In many cases, Ultracortenol had a beneficial subjective and objective effect which became apparent after five to six days. In cases of thromboangitis obliterans and of Raynaud's disease, the response was particularly rapid and pronounced. Inflammation and pain soon subsided, and cyanosis, "pins and needles," and hypothermia disappeared. Simultaneously, the nutritional state of the skin improved. The sense of touch increased. The intra-arterial injections of Ultracortenol were well tolerated. Re-examination many weeks later showed that the response had been maintained.

NEW MALIGNANT GROWTHS IN OLD AGE. SOME POINTS IN MORBID ANATOMY.

Howell, T. H., and Piggot, A. P. *Geriatrics* **13:** 176 (March) 1958.

At necropsy, carcinoma was found in 28.2 per cent of 2,221 subjects aged 65 years or older. The most common sites for new growths were the stomach (17.4 per cent), colon (16.4 per cent), bronchus (14.3 per cent), esophagus (9.1 per cent), and bile ducts and gallbladder (6.6 per cent). Increase of age in patients with carcinoma of the alimentary tract was associated with a gradual diminution in frequency of malignant disease. In the genitourinary tract, carcinoma occurred in the prostate in 3.4 per cent, in the bladder in 3 per cent, and in the kidney in 2.4 per cent of the patients. The 2 oldest patients in the series were a woman 101 years of age with carcinoma of the bronchus, and a woman 93 years of age with carcinoma of the colon. This analysis showed that a new growth could be present without causing death, and that this was particularly true in the later decades of life. In the oldest age groups, 2 malignant tumors were sometimes found in the same body. The new growths found in elderly subjects at necropsy appear to possess certain characteristics not found in those occurring in younger persons.

PEPTIC ULCER IN RHEUMATOID PATIENTS ON CORTICOSTEROID THERAPY. A CLINICAL, EXPERIMENTAL AND RADIOLOGIC STUDY.

Kammerer, W. H.; Freiberger, R. H., and Rivelis, A. L. *Arthritis & Rheumatism* **1:** 122 (Apr.) 1958.

In a study of the relation of adrenal steroid therapy to peptic ulcer, 14 healthy young adults with no history of gastro-intestinal disease received hydrocortisone in a dosage of

30 to 60 mg., or prednisone or prednisolone in a dosage of 7.5 to 10 mg. in varied sequence for two one-week periods. No changes occurred in the secretion of free hydrochloric acid or of pepsin that would seem to be significant in the genesis of peptic ulcer. Over a 12-month period, radiographic examinations of the upper gastro-intestinal tract were made in 117 patients with rheumatoid arthritis who were receiving corticosteroid therapy. Peptic ulcer was demonstrated in 36 of them—an incidence of 31 per cent. This contrasted with an incidence of 9 per cent among a group of patients who were not receiving corticosteroids, and of 5 per cent in patients not affected by rheumatoid arthritis. Of the 36 ulcers, 31 were gastric and 5 duodenal. The incidence of ulcer in both sexes was approximately the same, and greatest between the ages of 40 and 70 years. Neither the duration of the disease nor the duration of corticosteroid administration appeared to affect the development of peptic ulcer. Rather, the size of the dosage and the severity of the disease appeared to be significant factors, as more ulcers occurred in patients receiving larger amounts of steroid and in patients with severe arthritis. Thirty-two of the 88 patients receiving prednisone had an ulcer, 2 of 25 patients receiving triamcinolone, and 2 of 4 patients receiving cortisone. When an ulcer developed, an anti-ulcer regimen was instituted. There was little evidence, however, that the latter affected the rate of healing. In some patients whose disease was of such severity that withdrawing the drug would have returned them to a bedridden status, the steroid was continued as a calculated risk and with their knowledge of the hazards entailed. The use of a bland diet with frequent feedings proved to be the best way to avoid irritation of the gastric mucosa in these patients. Two unusual features of this study were 1) the finding of a preponderant occurrence of gastric rather than duodenal ulcer, and 2) the location of ulcer in the antrum of the stomach and on the greater curvature. Many of the ulcers were shallow and flexible upon palpation. It is postulated that corticosteroids may have an effect upon local tissue resistance and that this factor rather than changes in gastric secretion may account for the higher incidence of ulcer in patients receiving steroids.

RELATIONSHIP OF THE BLOOD PRESSURE TO WEIGHT, HEIGHT, AND BODY BUILD IN APPARENTLY HEALTHY SUBJECTS 65 TO 106 YEARS OF AGE.

Master, A. M., and Lasser, R. P. *Am. J. M. Sc.* **235:** 278 (March) 1958.

Data were gathered by means of questionnaires to physicians. The number of apparently healthy subjects accepted for analysis in the study was 5612, of which 2922 were males and 2690 females. The subjects of each sex were grouped according to height as short, average, or tall. Within each of these height groups they were divided into 4 weight groups (Underweight: 10 per cent lighter than the mean in the height group. Average: 9 per cent more or less than the mean in the height group. Moderately overweight: more than 10 per cent and less than 25 per cent above the mean for the height group. Severely overweight: 25 per cent more than the mean of the height group). In both sexes and in all height groups, the mean systolic and diastolic pressures were found to increase with increasing weight. Height alone bore little or no relation to blood pressure. The relative weight (that is, the weight in relation to height) rather than the absolute weight influences blood pressure. The average pressures found in males were as follows: underweight, 140/79; average weight, 145/81; moderately overweight, 148/84; severely overweight, 151/85. The average pressures found in females in these groups, respectively, were as follows: 151/82; 157/85; 158/86; and 160/88. It is concluded that obesity reduces the life span and that thin persons have the most favorable outlook with regard to life expectancy.

CIRCULATORY CHANGES IN CHRONIC LIVER DISEASE.

Murray, J. F.; Dawson, A. M., and Sherlock, Sheila, S. *Am. J. Med.* **24:** 358 (March) 1958.

The circulatory findings in 24 patients with portal cirrhosis were compared with results in 6 patients with biliary cirrhosis, 6 patients with extrahepatic portal vein obstruction,

and 14 normal subjects. Half of the patients with portal cirrhosis had a cardiac index above the upper limit of normal. Clinically, these patients had evidence of increased peripheral blood flow and ejection systolic murmurs. Roentgenographic or electrocardiographic changes were uncommon. Patients with biliary cirrhosis and portal-vein obstruction had normal cardiac indices. An increased total blood volume, mainly plasma volume, was found in patients with portal cirrhosis who had an increased cardiac index, a large portal-systemic collateral circulation, arterial oxygen desaturation and a low serum albumin level. The increased portal venous network did not account for the increased blood volume in portal cirrhosis, as patients with extrahepatic portal-vein obstruction had virtually normal blood volumes. The low serum albumin levels may in part represent the dilution of a normal amount of circulating albumin by an increased plasma volume. Four patients had low arterial oxygen saturation. Cardiac catheterization data in 1 patient and the results of studies in 2 others suggest that the arterial desaturation may be due to the shunting of blood through pulmonary arteriovenous anastomoses. One of these cases is presented in detail. In most patients with portal cirrhosis the increased cardiac output was tolerated without evidence of decomposition. Congestive heart failure was present in 1 patient reported in detail. As liver function and the clinical status of patients with portal cirrhosis improved, the cardiac output returned toward normal. The mechanism of production of the hyperdynamic circulatory state in portal cirrhosis is unknown. There is profound vasodilatation, and its mechanism is discussed. (From authors' summary.)

LA RESERPINA NEL TRATTAMENTO COLINERGICO DEL DIABETE MELLITO IN MALATI ARTERIOSCLEROTICI (THE CHOLINERGIC ACTION OF RESERPINE IN DIABETES WITH ARTERIOSCLEROSIS).

Nadel, M. B. J. *Gior. di Gerontol.* **6:** 107 (Feb.) 1958. (English abstract)

Through the use of reserpine it is possible to lower the requirement for insulin, overcome the resistance of the body to insulin, and overcome the hypersensitivity to insulin in aged diabetic patients. In large dosages, reserpine acts as a cholinergic agent (parasympathicotonically) in cases of diabetes with arteriosclerosis. Its sedative action is exerted upon the central nervous system and it is stronger than that of phenobarbital. The action of reserpine consists of releasing 5-hydroxytryptamine (enteramine or serotonin), an important hormone which is destroyed by such sympathicomimetic drugs as isopropyl-adrenaline. 5-Hydroxytryptamine favorably influences the evolution of diabetes in elderly people, as well as the arteriosclerosis (lowering the age index). In mild diabetes in elderly persons with blood sugar values up to 200 mg. per 100 ml., reserpine may cause a decrease of 10 to 60 mg. per 100 ml. It brings about improvement in severe cases with such signs and symptoms as acidosis, polyuria and polydypsia. Through its property of releasing 5-hydroxytryptamine, reserpine has an evident antidiuretic action in diabetes in elderly people. The dosage of reserpine used is 0.1 mg. three times daily, increased in six to seven days to the maximum individually tolerated dose (up to 1.75 mg. daily), which is maintained for six days. After a rest period of seven days, this 12-day dosage of reserpine is repeated, alone or in combination with insulin therapy. The administration of reserpine in diabetes with arteriosclerosis may be continued for years without inconvenience.

THE RELATION OF NONMALIGNANT POSTMENOPAUSAL ENDOMETRIAL CHANGES TO OVARIAN MORPHOLOGY.

Roddick, J. W., Jr., and Greene, R. R. *Am. J. Obst. & Gynec.* **75:** 235 (Feb.) 1958.

Data on 63 menopausal women were re-examined in order to determine whether any correlation existed between morphologic changes in the ovary, collectively known as "ovarian stromal hyperplasia," and findings in the nonmalignant postmenopausal endometrium that would indicate estrogen stimulation. It has been postulated that ovarian

stromal hyperplasia causes production of estrogen and that, in turn, estrogen accounts for the development of endometrial activity and ultimately carcinoma. Such changes in the ovary were found to be neither more nor less frequent in patients with active or inactive endometrium. Therefore, they are probably not accompanied by increased secretion of estrogen—at least not in amounts sufficient to stimulate the endometrium.

EXFOLIATIVE CYTOLOGY OF GASTRIC CARCINOMA.

Schade, R. O: K. *Brit. M. J.* **1:** 743 (Mar. 29) 1958.

Cytologic examination of gastric washings has made it possible to diagnose gastric carcinoma at an early stage when the tumor is confined to the mucosa. Two illustrative cases are presented. A study of the histories of patients with "surface carcinoma" has shown that these carcinomas develop slowly and that several years may elapse before the familiar type of carcinomatous tumor develops. The mucosa of the stomach will have undergone a profound structural alteration and some form of chronic atrophic gastritis will be present, often with widespread intestinal metaplasia. These findings led to the recommendation that patients with achlorhydria associated with structural mucosal changes such as a diffuse chronic atrophic gastritis be investigated to rule out the presence of carcinoma. The technic for obtaining the specimen for cytologic study is described. The characteristics of the malignant cell groups found show the following characteristics: 1) they often appear in clumps with the nuclei more closely approximated to each other or with overlapping of nuclei; 2) an irregular chromatin structure appears in the nuclei; 3) the nucleoli may be large and present in increased numbers; 4) the nuclear membrane stains intensively; 5) the nuclei may show hyperchromasia; 6) the nucleo-cytoplasmic ratio is altered in favor of the nucleus; 7) the cells vary greatly in size; and 8) the cytoplasmic outline may be indistinct. In addition, any of the following may be found in the smears: large numbers of polymorphs, plasma cells, fresh, diffusely distributed erythrocytes, and an abnormal bacterial flora which indicates the presence of achlorhydria.

AN EVALUATION OF MEPROBAMATE IN THE TREATMENT OF VARIOUS RHEUMATIC DISORDERS.

Steinberg, C. L., and Roodenburg, A. I. *Am. J. M. Sc.* **235:** 157 (Feb.) 1958.

Meprobamate was used in the treatment of 64 patients with various rheumatic disorders. In 8 patients (Group A), the rheumatoid arthritis or osteoarthritis was complicated by manifestations of an anxiety neurosis. These cases were studied to detect any change in the level of serum cholesterol and protein, but none was found; and no objective improvement occurred in the joints. Four patients were also receiving small doses of prednisone, and 4 others 100 to 300 mg. of phenylbutazone per day. Group B contained 6 patients as follows: psychogenic rheumatism, 1; palindromic rheumatism, 1; malum coxae senilis, 1; rheumatoid arthritis, Stage IV, 1; and osteoarthritis, 2. No changes occurred in the potassium, sodium, carbon dioxide, and chloride levels when these were studied during the administration of 1200 mg. of meprobamate daily. The patient with psychogenic rheumatism had complete relief of all symptoms referable to the joints, and the patient with malum coxae senilis had less pain and stiffness of the hips, but the remaining 4 patients were not benefited. Among the 50 patients in Group C, 26 had psychogenic rheumatism. Twenty-two of these patients had a satisfactory clinical response to meprobamate alone. Meprobamate added to antirheumatic therapy in patients with organic disease of the joints produced no added benefit. The dosage ranged from 200 mg. three times daily to 400 mg. four times daily in this group of patients. The side-actions observed in this study were: somnolence, 40 patients; dizziness, 5; severe gastric distress, 1; unsteady gait, 1; fullness in the head, 3; and skin rash, 1. It is concluded that meprobamate is useful in the treatment of psychogenic rheumatism and is more safe than many drugs now employed in rheumatic disorders.

ROLE OF INSULIN IN ACUTE HYPOGLYCEMIC ACTION OF TOLBUTAMIDE.

Weaver, J. A.; Prout, T. E.; Scott, G. W., and Asper, S. P. *Brit. M. J.* **1:** 425 (Feb. 22) 1958.

Ten patients with diabetes mellitus of recent onset, not controlled by diet or previously treated with insulin, were given a single dose of 3 Gm. of tolbutamide orally. Eight of these 10 patients showed a significant fall in the glucose concentration of venous blood. Studies on the difference between the arterial (A) and venous (V) blood glucose concentrations, expressed as A-V/A, showed no evidence of an increase in the uptake of glucose by the peripheral tissues in patients given tolbutamide. Studies of the insulin-like activity of serum, as assayed by the rat hemi-diaphragm method, showed that there is no change in the insulin-like activity in the patients' serum before and after tolbutamide administration. The rate of disappearance of intravenously administered insulin-I^{131} from plasma was studied in normal rabbits by the electrophoretic technic. No difference in the rate of disappearance of insulin-I^{131} was found following the injection intravenously of tolbutamide, as compared with the rate in untreated animals. These studies support the view that the hypoglycemic action of tolbutamide is not produced by an increase in the effective level of insulin. (From authors' summary.)

PSYCHOSOMATIC FACTORS IN THE MENOPAUSE.

Wright, G. J., Jr. *Pennsylvania M. J.* **61:** 349 (March) 1958.

No single psychopathologic entity occurs at the menopausal period. Although the nervous symptoms in some women may be caused by an endocrine imbalance, emotional illnesses during the menopause are not directly related to glandular deficiency but result from the patient's reaction to psychologic, physical and environmental changes taking place at this time. Among the factors that predispose to or precipitate illness are fear of the menopause, the end of the child-bearing period, physical changes, psychosexual problems, a feeling of uselessness when children are grown and household duties may no longer consume much time, the loss of parents, the realization of an empty life facing a spinster particularly when she has cared for younger brothers and sisters or her parents, or the feeling of frustration in a career woman when she has exhausted the possibilities for advancement. The proper treatment is prophylactic. An understanding of the ways in which a woman feels threatened will assist in planning management. She should be given an explanation of the physiologic changes taking place at the menopause. A healthy and scientific attitude is essential to satisfactory treatment. No pelvic surgery should be undertaken until the physician and surgeon understand what the operation means to the patient and have corrected any misconceptions, allayed any fears about it, and explained the results that may be anticipated. Drugs administered with the aim of overcoming the hormonal deficiency are unlikely to relieve the various forms of emotional instability. Sedatives may prove useful to the psychiatrist in patients in whom hormones have proved inadequate in relieving symptoms. The simplest problems may respond to management by careful physical examination and treatment of minor physical symptoms, but it may become necessary to find the reason for conflict or stress and to seek a solution to the particular problem. The general practitioner, through his knowledge of the family, is in a favorable position to suggest any necessary changes in environment. With adequate preparation and understanding, most women will experience no difficulty at the menopause. The development of personality assets and of interests for the use of leisure time will prove to be rewarding pursuits.

BOOKS RECEIVED

Receipt of the following books for review is hereby acknowledged. We are glad to publish complete listings of all new books received but such listing must be regarded as a sufficient return for the courtesy of the sender. Books of particular interest will be reviewed in full as time and space permit. Additional information in regard to all listed books will be gladly furnished upon request.

THE BRAIN AND HUMAN BEHAVIOR. Proceedings of the Association for Research in Nervous and Mental Disease, December 7 and 8, 1956, New York, N. Y. Editors: *Harry C. Solomon, M.D., Stanley Cobb, M.D.* and *Wilder Penfield, M.D.* Cloth. $15.00. Pp. 564. 200 Illustrations. 53 Tables. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents, 1958.

REHABILITATION OF THE CARDIOVASCULAR PATIENT. By *Paul Dudley White, M.D.*, Massachusetts General Hospital, Boston; *Howard A. Rusk, M.D.*, Professor and Chairman, Department of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, New York; *Philip R. Lee, M.D.*, Department of Internal Medicine, Palo Alto Clinic, Palo Alto, California; and *Bryan Williams, M.D.*, Clinical Instructor in Medicine, The University of Texas, Southwestern Medical School, Dallas. Cloth. $7.00. Pp. 176. McGraw-Hill Book Company, Inc. (Blakiston Division), New York, 1958.

POLYMYOSITIS. By *John N. Walton, M.D., M.R.C.P.*, First Assistant in Neurology, King's College, University of Durham, in the Royal Victoria Infirmary, Newcastle upon Tyne; late Nuffield Foundation Fellow in Neurology and Neuropathology, Harvard Medical School and Massachusetts General Hospital, Boston, Mass.; and King's College Travelling Fellow in the Neurological Research Unit, the National Hospital, Queen Square, and *Raymond D. Adams, M.D.*, Bullard Professor of Neuropathology, Harvard University and Chief of the Neurological Service, Massachusetts General Hospital, Boston, Mass. Cloth, $7.00. Pp. 270. E. & S. Livingstone Ltd., Edinburgh and London, 1958. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents.

PORTAL HYPERTENSION. Jacksonian Prize Essay, Royal College of Surgeons 1956. By *Alan Henderson Hunt, M.A., D.M., M.Ch., F.R.C.S.*, Surgeon, St. Bartholomew's Hospital and The Royal Marsden Hospital; late Hunterian Professor, Royal College of Surgeons of England. Cloth. $8.50. Pp. 230. E. & S. Livingstone Ltd., Edinburgh and London, 1958. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents.

CHEMISTRY AND BIOLOGY OF MUCOPOLYSACCHARIDES—Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.*, and *Maeve O'Connor, B.A.* Cloth. $8.50. Pp. 323. 48 Illustrations. Little, Brown and Company, Boston, Massachusetts, 1958.

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Books for review should be sent to Edward Henderson, M.D., Editor-in-Chief, 236 Midland Avenue, Montclair, N. J.

NEWS AND NOTICES

POSTGRADUATE PROGRAM ON MEDICAL PROBLEMS OF THE ELDERLY

The University of Texas Postgraduate School of Medicine will present a two and one-half day program on "Medical Problems of the Elderly" *October 23, 24 and 25, 1958*. Visiting lecturers for the program include Dr. Roger S. Mitchell, Denver, Colorado; Dr. Edward C. Reifenstein, Jr., Butler, New Jersey; Dr. Jack Weinberg, Chicago, Illinois; Dr. E. L. Bortz, Philadelphia, Pennsylvania; Dr. Herbert Rattner, Chicago, Illinois; and Dr. Michael M. Dacso, New York, New York.

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